dermite affectant des Indiens de l'Amérique du Nord se transmette suivant un trait d'autosome dominant.

La photodermite qui se produit chez les Indiens de l'Amérique du Nord ressemble à l'exanthème polymorphe du reste de la population. Elle est différente quant à l'hérédité, le commencement précoce, sa persistence pendant l'hiver et aussi parce qu'elle se produit quelquefois comme une cheilite grave et chronique de la lèvre inférieure.

REFERENCES

1. Manitoba Department of Agriculture and Conservation, Social and Economic Research Office: A study of the population of Indian ancestry living in Manitoba, undertaken under the direction of J. H. Lagasse, Queen's Printer, Winnipeg, 1959.
2. SCHENCK, R. R.: *J. A. M. A.*, **172**: 1134, 1960.
3. EVERETT, M. A. *et al*: *Arch. Derm. (Chicago)*, **83**: 243, 1961.
4. LAMB, J. H. *et al.*: *Arch. Derm. Syph. (Chicago)*, **62**: 1, 1950.
5. BRANDT, R.: *A.M.A. Arch. Derm.*, **77**: 581, 1958.
6. RENTIERS, P.: Personal communication.
7. ROY, A. K.: Personal communication.
8. JACKSON, R.: Personal communication.
9. EPSTEIN, J. H.: *Arch. Derm. (Chicago)*, **85**: 82, 1962.

Effect of Methandrostenolone on Blood Lipids and Liver Function Tests

MAURICE VERDY, M.D., F.R.C.P.[C],*
LEON TETREAULT, M.D., M.Sc.(Pharm.), F.C.P.C.,†
WALTER MURPHY, M.D.‡ and LOUIS PERRON, M.D.,§ *Montreal*

ANABOLIC steroids are widely used. Their effect on blood lipids has been described in several publications. So far as methandrostenolone¶ is concerned, some authors have reported an increase in blood cholesterol,[1-3] others have noted no effect[4, 5] and still others have observed a decrease.[6-8] Since it is now considered desirable to avoid hypercholesterolemia in the presence of atherosclerosis, it seemed important to us to examine the effect of methandrostenolone on blood lipids in more detail, particularly since anabolic agents are prescribed primarily for that age group in which atherosclerosis is common.

We chose to examine the effect of methandrostenolone in a group of aged and atherosclerotic patients, using the therapeutic doses usually recommended for such patients in Canada (i.e., 5 to 10 mg. daily, for short periods of time) and also the somewhat higher doses common in Europe.

SUBJECTS AND METHODS

Eighteen males from a hospital for the chronically ill were selected as the subjects of the study. A diagnosis of atherosclerosis had been made in the majority of the cases. Three different treatment schedules, each of three periods of three weeks' duration, were drawn up, and six patients were assigned to each treatment schedule by means of a random number table. A description of the patients in the three groups is given in Table I, and their treatment schedules are described in Table II. The double-blind technique was used throughout the study.

The biochemical analyses were performed at the Laboratoire de Recherches d'Endrocrinologie et de Nutrition of the Hôtel-Dieu de Montréal, utilizing the following methods: bromsulphalein (BSP)—5 mg. per kg. was injected intravenously, blood being then withdrawn at two different times, 0 and at 45 minutes for estimation of the excretion test; the prothrombin time was performed at the bedside, on whole blood, using activated thromboplastin;[9] serum transaminases by means of the Hyland kit;[10] triglycerides by the method of Van Handel and Zilversmit;[11] total and esterified cholesterol by the method of Zak *et al.*,[12] modified; phospholipids by the method of Fiske and Subbarow,[13] modified; total lipids were calculated by adding together the various lipid fractions; non-esterified fatty acids (NEFA) by the method of Dole,[14] modified. All the analyses were done at the beginning of the study and repeated every three weeks (i.e. at the end of each period) except for the BSP, which was done only twice (at the beginning and at the end of the study).

From the Section d'Endocrinologie et de Nutrition, Hôtel-Dieu de Montréal; the Medical Department, CIBA Company Limited, Dorval, Quebec; and the Département de Pharmacologie, Université de Montréal, Montreal, Quebec.
*Assistant-Professeur, Université de Montréal, Section d'Endocrinologie et de Nutrition, Hôtel-Dieu de Montréal, Montreal, Quebec.
†Assistant-Professeur, Département de Pharmacologie, Université de Montréal.
‡Medical Adviser, CIBA Company Limited, Dorval, Quebec.
§Résident en Médecine, Hôtel-Dieu de Montréal.
¶Methandrostenolone is $\Delta 1$, 17_α-methyltestosterone (Danabol, CIBA).
Reprint requests to: Dr M. Verdy, Hôtel-Dieu de Montréal, 3840 rue St-Urbain, Montréal 18, Québec.

TABLE I.—LIST OF SUBJECTS

Patient	Age	Diagnosis	Cholesterol (total) mg. per 100 ml.	Triglycerides mg. per 100 ml.	Phospholipids mg. per 100 ml.	BSP retention at 45 min. %
	Group 1 (P-P-P)					
1	60	Parkinsonism	251	162	273	11.3
2	78	Cerebral AS	228	215	300	26
3	67	AS, CVA; alcoholism	265	274	345	39
4	60	CVA	318	196	333	12
5	59	Multiple sclerosis	400	192	362	4.7
6	68	CVA, diabetes	208	229	257	56
	Group 2 (M5-P-M5)					
7	62	AS, parkinsonism	310	164	368	5
8	76	AS	240	205	322	8
9	78	CVA, AHD	318	196	333	12
10	66	CVA	241	137	322	7.3
11	73	Tabes	206	145	268	3.4
12	83	AS, blindness	271	139	316	8
	Group 3 (M10-M10-M10)					
13	70	AS, lues	191	226	289	4
14	72	AHD	245	141	316	14
15	76	Diabetes, AS, CVA	180	113	232	23
16	76	CVA	356	117	380	3.9
17	58	Mental debilitation	239	101	278	5.0
18	74	Diabetes	276	93	300	48

AS: atherosclerosis CVA: cerebrovascular accident AHD: atherosclerotic heart disease

Descriptive statistical methods (the mean and standard error of the mean), calculated for each group, were used in the analyses of the effects of the three treatment schedules on the parameters studied. In this chronological evaluation, each subject is always considered as his own control. The number of patients in each group being rather small, no comparative statistical analysis was performed to establish statistically significant differences between treatments.

TABLE II.—TREATMENT SCHEDULES

Group	First period (3 weeks)	Second period (3 weeks)	Third period (3 weeks)
1 (six patients)	P	P	P
2 (six patients)	M5	P	M5
3 (six patients)	M10	M10	M10

During each period, patients received either P (consisting of 2 tablets of placebo) or M5 (consisting of 1 tablet of methandrostenolone 5 mg. plus 1 tablet of placebo) or M10 (consisting of 2 tablets of methandrostenolone 5 mg.).

RESULTS

1. *Transaminases*

The results of serum glutamic pyruvic transaminases (SGPT) are given in Table III and the same results are illustrated in Fig. 1. In the two groups that received methandrostenolone the mean values are seen to increase. The increase, however, was not constant and tended to return toward normal despite continued therapy. Indeed it was present in only three of the six patients who received methandrostenolone throughout the study (10 mg. daily). In these patients, after three weeks, SGPT values went up to 175 in one, 200 in another and 232 units in the third and then decreased to 57, 147 and 29 units. In the group that received methandro-

TABLE III.—EFFECT ON SGPT (UNITS)

Treatment	Before treatment mean ± S.E.M.	3rd week mean ± S.E.M.	6th week mean ± S.E.M.	9th week mean ± S.E.M.
GR. 1 (P, P, P)	15 ± 2.2	12 ± 2.7	10 ± 1.9	10 ± 2.8
GR. 2 (M_5, P, M_5)	14 ± 1.0	68 ± 20.4	10 ± 2.1	24 ± 4.8
GR. 3 (M_{10}, M_{10}, M_{10})	18 ± 2.8	109 ± 42.3	73 ± 31.5	45 ± 21.5

The data given here are presented graphically in Fig. 1.

TABLE IV.—EFFECT ON LIVER FUNCTION TESTS

Treatment	*Group 1 (P, P, P)*		*Group 2 (M_5, P, M_5)*		*Group 3 (M_{10}, M_{10}, M_{10})*	
Time	*Before treatment*	*After treatment*	*Before*	*After*	*Before*	*After*
	mean ± S.E.M.	*mean ± S.E.M.*	*mean ± S.E.M.*	*mean ± S.E.M.*	*mean ± S.E.M.*	*mean ± S.E.M.*
B.S.P. (% retention after 45 minutes)	25 ± 8.0	11 ± 4.1	7 ± 1.2	10 ± 1.6	16 ± 7.0	32 ± 5.1
S.G.P.T. (units)	15 ± 2.2	10 ± 2.8	14 ± 1.0	24 ± 4.8	18 ± 2.8	45 ± 21.5
S.G.O.T. (units)	27 ± 2.2	10 ± 0.8	25 ± 1.3	14 ± 1.2	28 ± 4.0	23 ± 8.2
Prothrombin (per cent)	99 ± 2.3	98 ± 2.3	98 ± 1.2	100 ± 0	95 ± 2.2	98 ± 3.2

The values given here are the values before treatment and those at the end of the study (9th week).

stenolone 5 mg. daily during the first and last periods, four of six patients showed an increase in SGPT and when the drug was interrupted at the end of the first period in that group, the SGPT values returned to normal. When methandrostenolone was again administered (third period of the study), the mean SGPT increased only slightly, but again two patients (the same two as before) showed absolutely no increase.

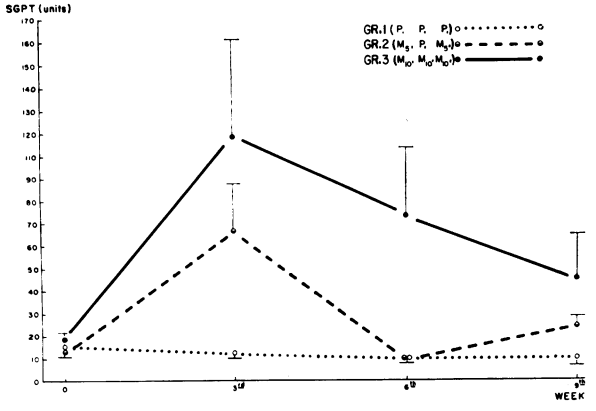

Fig. 1.—Each value is the mean of six patients: the vertical lines indicate the standard errors of the mean (S.E.M.). Note the increase in transaminases with treatment: the maximum increase in group M10, M10, M10 is at the 3rd week, but the values come back toward normal in spite of the continuation of treatment. The data from which this figure is constructed are given in Table III.

No changes in transaminase values were seen in the placebo group.

The results for the serum glutamic oxaloacetic transaminases (SGOT) are similar to those for the SGPT (in Table IV part of the results are given).

2. *Bromsulphalein Excretion Test*

Before treatment, the BSP retention values were abnormal in the majority of the patients (Table I). Furthermore, in Table IV it is seen that the mean values for the three groups before treatment were different (25%, 7% and 16%); therefore the population studied was not homogeneous in that respect. The mean BSP value for the group receiving placebo (P.P.P.) was lower at the end of the study, 11%, as compared to 25% at the beginning of the study; in the second group (M5.P.M5) it did not change, 10%, as compared to 7%; and in the third group (M10. M10.M10) the mean value was higher at the end, 32%, as compared to 16% at the beginning.

3. *Lipids*

The total cholesterol values for each period of the study are given in Table V; the same data are illustrated in Fig. 2. In all three groups there is a general trend for the cholesterol to decrease, but the differences observed are not important.

The results for all the lipid fractions measured, at the beginning and at the end of the study, are given in Table VI. All the lipid fractions (except the NEFA) decreased during the study in the three groups. For the triglycerides, the mean value for the group that received methandrostenolone 10 mg. was different from the mean of the placebo group, both at the beginning and at the end of the study. Therefore, we cannot say that methandrostenolone caused a decrease in triglycerides. None of the changes in the other lipid fractions are significant.

TABLE V.—EFFECT ON TOTAL CHOLESTEROL (MG. PER 100 ML.)

	Before treatment	*3rd week*	*6th week*	*9th week*
Treatment	*mean ± S.E.M.*	*mean ± S.E.M.*	*mean ± S.E.M.*	*mean ± S.E.M.*
GR. 1 (P,P,P)	278 ± 28.7	239 ± 8.6	260 ± 21.4	251 ± 24.4
GR. 2 (M_5, P, M_5)	257 ± 14.7	207 ± 8.1	226 ± 20.7	217 ± 15.0
GR. 3 (M_{10}, M_{10}, M_{10})	246 ± 25.8	202 ± 22.3	194 ± 27.2	209 ± 22.6

The data given here are presented graphically in Fig. 2.

TABLE VI.—EFFECT ON BLOOD LIPIDS

Treatment	*Group 1 (P, P, P)*		*Group 2 (M_5, P, M_5)*		*Group 3 (M_{10}, M_{10}, M_{10})*	
Time	*Before treatment*	*After treatment*	*Before*	*After*	*Before*	*After*
	mean ± S.E.M.	*mean ± S.E.M.*	*mean ± S.E.M.*	*mean ± S.E.M.*	*mean ± S.E.M.*	*mean ± S.E.M.*
Total lipids (mg./100 ml.)	801 ± 44.9	658 ± 50.5	741 ± 31.9	603 ± 43.5	711 ± 32.0	562 ± 44.6
Total cholesterol (mg./100 ml.)	278 ± 28.7	251 ± 24.4	257 ± 14.7	217 ± 15.0	246 ± 25.8	209 ± 22.6
Esterified cholesterol (mg./100 ml.)	210 ± 23.7	184 ± 20.0	193 ± 15.0	158 ± 11.5	176 ± 23.8	137 ± 19.8
Triglycerides (mg./100 ml.)	211 ± 15.6	165 ± 9.2	160 ± 10.7	138 ± 11.7	132 ± 11.0	120 ± 7.0
Phospholipids (mg./100 ml.)	312 ± 17.0	254 ± 14.6	324 ± 13.6	248 ± 21.1	299 ± 19.9	234 ± 20.8
NEFA (mEq./litre)	0.635 ± 0.065	0.605 ± 0.043	0.658 ± 0.065	0.725 ± 0.148	0.717 ± 0.090	0.555 ± 0.110

The values given are those obtained before and at the end of the study (9th week). The total cholesterol data are given in more detail in Fig. 2 and Table V. The decrease in lipid fractions during the study was similar in the three groups.

DISCUSSION

Reports concerning the effect of methandrostenolone on blood lipids, especially cholesterol, are contradictory. Several factors probably contribute to these differences in results, including the doses used,[15] the state of health of the subjects, their age and seasonal fluctuations in cholesterol levels.

In this study the doses used were those recommended for use in debilitating diseases. In the study of Jose and Mitchell,[1] where a hypercholesterolemia was observed with methandrostenolone, the daily dose was 15 mg. Stone[7] used doses varying between 10 and 25 mg. daily. It is interesting to note that although his report is entitled "Elevation of Serum Cholesterol by an Anabolic Steroid", of four patients suffering from essential familial hyperlipemia, only two showed an increase in cholesterol levels, whereas the other two showed a significant decrease. Moreover, the most marked change was a large decrease in the triglycerides, which occurred following treatment with methandrostenolone.

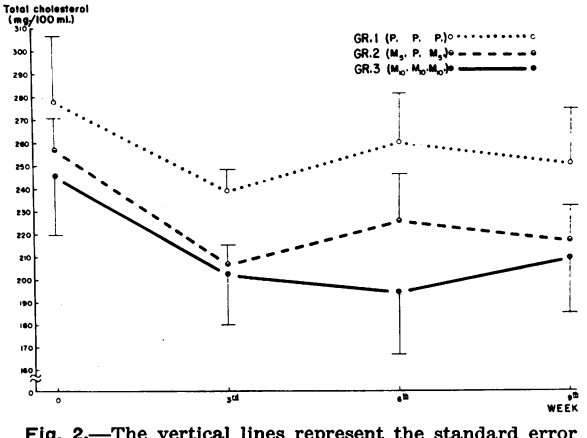

Fig. 2.—The vertical lines represent the standard error of the mean. Note the trend towards a decrease in each of the groups. At the 9th week there is no significant difference between the means of the three groups. The data from which this figure is constructed are given in Table V.

The age of the subjects may be of some importance. Our study involved aged patients, since the drug in question is frequently prescribed for this age group. It can be seen (Table I) that five patients had a cholesterolemia of more than 300 mg. per 100 ml. at the beginning of the study, and more than half of the patients had triglyceride values in excess of 150 mg. per 100 ml. Some studies[1] would seem to indicate that an increase in cholesterol levels after the administration of methandrostenolone is usually seen, particularly in those patients whose cholesterol levels are above normal at the time of starting the medication. In our study, the three hypercholesterolemic patients, (7, 9 and 16) who received methandrostenolone followed the trend of the rest of the group.

In the course of the present study a decrease of all the lipid fractions was seen, even in the control group. A possible explanation for this phenomenon might perhaps be the seasonal variations described by Thomas, Holljes and Eisenberg[16] in a group of young normal males. These authors observed that total cholesterol values reach a maximum in December and January and a minimum during the summer. It is possible that these variations might be greater in aged and atherosclerotic patients. Our study began in May and ended in July.

It has been convincingly demonstrated previously[17] that BSP retention is frequently increased during the administration of most of the testosterone derivatives, including methandrostenolone. It is probable that the increased retention reflects a defect in elimination of the dye without there being any accompanying

hepatic damage. Studies by means of the electron microscope have revealed that some alterations in the biliary canaliculi may occur under these conditions.[18] The BSP values for the group receiving methandrostenolone throughout our study (10 mg. daily) were more abnormal at the end of the study than at the beginning. During the same time the placebo group showed an important change in the other direction, from a control of 24% to 11%, which suggests the possibility of variations due to unknown factors. When the drug was continued for longer periods of time, a return to normal was seen. The temporary elevation of the transaminase observed here is also similar to that reported by Wynn, Landon and Kawerau.[19] As far as the transaminase increase is concerned, the variation between individuals is intriguing and cannot be explained. It is interesting also that in the group receiving methandrostenolone throughout, the three patients who showed no increase in transaminase levels were the three patients who had abnormal BSP excretion tests before the study (patients 14, 15, 18). This may not be a constant finding, but it demonstrates that patients with evidence of previous liver damage are not more likely to have an increase in transaminase levels.

Summary Using the double-blind technique, methandrostenolone, 5 or 10 mg. daily, or a placebo, was administered to 18 males (average age: 69) in a hospital for the chronically ill. At the conclusion of the study, which lasted nine weeks, no differences were observed between the control and treatment groups with respect to the level of blood lipids. Alterations in the bromsulphalein excretion times and in the serum glutamic transaminases resembled those already reported by other authors.

Résumé Dans un hôpital pour malades chroniques, 18 hommes (moyenne d'âge 69 ans) ont reçu, à double insu, méthandrostenolone, 5 mg. ou 10 mg. par jour, ou placebo. A la fin de l'étude qui dura neuf semaines, nous n'avons pas observé de différences dans le taux des lipides sanguins entre les groupes traités et le groupe témoin. Les changements de la BSP et des transaminases sériques sont semblables à ceux déjà rapportés par plusieurs auteurs.

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REFERENCES

1. JOSE, A. D. AND MITCHELL, A. S.: *Lancet*, 1: 473, 1964.
2. WERNER, M. *et al.*: *Klin. Wschr.*, 39: 1006, 1961.
3. LANDON, J. *et al.*: *Metabolism*, 11: 501, 1962.
4. LOIODICE, L. AND VENTURA, E.: *Bull. Soc. Med. Chir. Modeno*, 3: 591, 1964.
5. BLOOM, A. AND GLICK, J.: Personal communication.
6. LEON, N.: *An. Paul. Med. Cir.*, 81: 146, 1961 (abstract).
7. STONE, M. C.: *Lancet*, 1: 725, 1964.
8. FURMAN, R. H. AND HOWARD, R. P.: *Ibid.*, 1: 837, 1963.
9. COLPRON, G. AND LONG, L.: Unpublished data.
10. REITMAN, S. AND FRANKEL, S.: *Amer. J. Clin. Path.*, 28: 56, 1957.
11. VAN HANDEL, E. AND ZILVERSMIT, D. B.: *J. Lab. Clin. Med.*, 50: 152, 1957.
12. ZAK, B. *et al.*: *Amer. J. Clin. Path.*, 24: 1307, 1954.
13. FISKE, C. H. AND SUBBAROW, Y.: *J. Biol. Chem.*, 66: 375, 1925.
14. DOLE, V. P.: *J. Clin. Invest.*, 35: 150, 1956.
15. LIDDLE, G. W. AND BURKE, H. A., JR.: *Helv. Med. Acta*, 27: 504, 1960.
16. THOMAS, C. B., HOLLJES, H. W. D. AND EISENBERG, F. F.: *Ann. Intern. Med.*, 54: 413, 1961.
17. FOSS, G. L. AND SIMPSON, S. L.: *Brit. Med. J.*, 1: 259, 1959.
18. SCHAFFNER, F. AND KNIFFEN, J. C.: *Ann. N.Y. Acad. Sci.*, 104: 847, 1963.
19. WYNN, V., LANDON, J. AND KAWERAU, E.: *Lancet*, 1: 69, 1961.