DEVELOPMENT OF HIRSUTISM AFTER PUBERTY*

BY

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[WITH SPECIAL PLATE]

The problem of the development of hirsutism after puberty is of great medical importance, and an understanding of its causes is therefore necessary. At the present time it seems that the condition may be divided into three main categories: (1) associated with adrenal cortical dysfunction of demonstrable proportions, such as that seen in the adreno-genital syndrome (Wilkins *et al.*, 1955) or in adreno-cortical tumours; (2) Stein-Leventhal syndrome; and (3) simple (idiopathic or constitutional) hirsutism. Much comment has been made on the last of these conditions (Dorfman and Shipley, 1956), whereas the Stein-Leventhal syndrome is much less known; even Stein accumulated only 75 cases in a period of 20 years (Stein *et al.*, 1949). The most popular view at present is that some androgenic substance may be derived from the ovary of these patients (Plate, 1951) and that theca luteinization is of importance in the ovarian pathology (Culiner and Shippel, 1949). In this communication emphasis is laid upon the problems of diagnosis and aetiology, including an examination of the biochemical features of the steroids found in the urine, both with and without stimulation of the adrenal cortex by corticotrophin.

Present Series

The cases here presented were all characterized by the development of hirsutism after puberty. Clinical analysis of the group (Table I) shows that it may be subdivided. The ultimate criterion for the diagnosis of the Stein-Leventhal syndrome was examination of portions of the ovaries after operation. In some instances the size of the ovary and appearance of the capsule were almost normal. Indeed, the impression is gained that only minimal enlargement, if any enlargement at all, need be present. In one instance the ovaries reached nearly three times normal size. Microscopically, persistent follicles were always identified,

TABLE I.—Diagnostic Classification of Cases of Post-pubertal Hirsutism

	No. of Cases
"Hirsutism" (? cause; previous encephalitis, 2)	32
Stein-Leventhal syndrome	9
? Stein-Leventhal syndrome	7
Adrenal virilism	1
Total	49
Adrenal cortical carcinoma	1

with a tendency to cyst formation, and proliferation and luteinization of the theca interna was present (Special Plate, Fig. 1).

Indications for laparotomy in these patients have been sterility or severe menstrual irregularity associated with

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hirsutism, except in one instance where pain at menstruation was the immediate reason for operation. There have been clinical indications of at least a minor degree of ovarian enlargement. This evidence was obtained by vaginal examination with relaxation under anaesthesia, and confirmed, in all instances where it was done, by x-ray visualization after induction of pneumoperitoneum (Table II; Special Plate, Fig. 2). The dose of x rays involved is only 200 milliroentgens and has been considered negligible in the circumstances.

Examination of Table II will show that the patients with Stein-Leventhal ovaries were characterized by certain features, including the usual ones of sterility and menstrual irregularity. Ovulation, mental depression, and a family history of hirsutism were absent in comparison with the group designated as "hirsutism." This group of 32 patients

TABLE II.—Differentiating Features of "Hirsutism" and Stein-Leventhal Syndrome with Hirsutism

	"Hirsutism"	Stein-Leventhal Syndrome	? Stein-Leventhal Syndrome
Total cases	32	9	7
Irregular menses	8	9	6
Sterility	2 (8)	6 (6)	2 (7)
Ovulation (temp.)	4 (4)	0 (3)	—
Vaginal examination under anaesthetic: positive results	6 (13)	9	3 (5)
Pelvic radiograph positive	2 (5)	6 (6)	? 1 (4)
Mental depression	10	1	0
Family history of hirsutism	7	0	1

Figures in parentheses in this and subsequent tables indicate number of patients observed where this was less than total in group.

remained after deducting those patients with other diagnoses as indicated in Table I. The group of patients designated as likely cases of Stein-Leventhal syndrome did not have a laparotomy performed. They were separated on account of their lack of fertility and their menstrual history, and otherwise resemble the Stein-Leventhal group.

Among the "hirsutism" group ovulation tended to be present. Of the six cases with suspicious ovaries as shown by vaginal examination, four had irregular menses and in one case normal ovaries were found on laparotomy. This was the only instance where laparotomy has been performed with negative ovarian findings. Of the two cases with possible ovarian enlargement as seen radiographically, one had

TABLE III.—Features of Similarity in "Hirsutism" and Stein-Leventhal Syndrome

	"Hirsutism"	Stein-Leventhal Syndrome	? Stein-Leventhal Syndrome
Total cases	32	9	7
Severe hirsutism	11	2	1
Age of onset of hirsutism (years)	11-35 (Under 18 in 19 patients)	12-24	12-24
Obesity	15	4	4
Acne	5	2	1
Enlarged clitoris	1	0	0
Hypertension	4	0	0

irregular menses and the other was the patient mentioned with normal ovaries. Of the eight patients with irregular periods, two at least may have Stein-Leventhal ovaries, so that here is clinical evidence that even this group of patients may not be quite homogeneous. In Table III are presented the characters which appeared common to all groups. There was, and especially among the "hirsutism" group, a strong tendency for hirsutism to appear in the years just after establishment of menstruation. Somewhat surprisingly, obesity was equally distributed among the patients, and therefore seems not to be a useful indication of the possible presence of the Stein-Leventhal syndrome. It should be noted that one of the group of "hirsutism" patients had an enlarged clitoris, and this point will again be referred to below.

Studies of Urinary Steroids

Resting Excretion

The excretion of ketogenic steroids as determined by minor modifications of the method of Norymberski *et al.* (1953) was normal in all groups of patients. In the

TABLE IV.—Resting 17-Ketosteroids and Ketogenic Steroids

	No. of Patients	17-Ketosteroids (mg. per day)	Ketogenic Steroids (mg. per day)
"Hirsutism"	32	13.8 ± 0.61 (S.E.)	11.5 ± 0.83 (25)
Stein-Leventhal syndrome ..	6	10.5 ± 1.02 (P = < 0.05)	8.9 ± 1.08
? Stein-Leventhal syndrome ..	7	10.1 ± 0.60 (P = < 0.01)	11.4 ± 1.27

"hirsutism" group the mean 17-ketosteroid level was above the normal average of 10 mg., and significantly above the mean of the Stein-Leventhal group (P=0.05) and the "? Stein-Leventhal" group (P=0.01) (Table IV). It will be seen from the accompanying diagram that there was a wide scatter of 17-ketosteroid levels in the "hirsutism" group. These determinations were made by the techniques of Gibson and Norymberski (1954).

Diagram showing correlation between resting 17-ketosteroids and 17-ketosteroid response to four-day test with corticotrophin. The dotted lines indicate the upper normal ranges.

Response to Corticotrophin

Corticotrophin was injected in the form of gel in a dosage of 20 U.S.P. units intramuscularly twice daily for four days according to the method previously described (Prunty, 1956). Two batches of corticotrophin of known potency (89754 and P 80205) were used. The figures in Table V are the means of the highest figures reached during this test, usually those of the third or fourth day. The values for a control group of 15 women unaffected by hirsutism and of similar age are included. None of the patients under study differed from normal in the excretion of ketogenic steroids. The "hirsutism" group gave a mean for 17-ketosteroids significantly greater than normal (P=<0.01), and for the ratio ketogenic steroids/17-ketosteroids significantly less than normal (P=<0.01). The "? Stein-Leventhal" group gave a mean figure for 17-ketosteroids possibly significantly less than the "hirsutism" group (P=<0.05), but this was not true of the Stein-

TABLE V.—Steroid Response to Corticotrophin

	No. of Subjects	Ketogenic Steroids (mg. per day)	17-Ketosteroids (mg. per day)	Ratio Ketogenic Steroids/17-Ketosteroids
Controls	16	68.7 ± 6.9 (S.E.)	22.3 ± 1.95	3.24 ± 0.30
"Hirsutism"	25	67.6 ± 5.0	40.4 ± 3.0	1.80 ± 0.17
Stein-Leventhal syndrome ..	5	74.4 ± 14.0	32.2 ± 4.8	2.31 ± 0.37
? Stein-Leventhal syndrome ..	6	65.2 ± 15.3	26.5 ± 3.2	2.36 ± 0.43

Levels of significance for ketosteroid means: hirsutism/controls, P = < 0.01; ? Stein-Leventhal syndrome/hirsutism, P = < 0.05; Stein-Leventhal syndrome/hirsutism, P = > 0.05. For K.G.S./K.S. ratio, hirsutism/controls, P = < 0.01.

Leventhal group (P=>0.05). It should be emphasized that both these groups are small, as can be seen from the Table. A significant correlation was observed between the resting 17-ketosteroids and the level after corticotrophin injection in the "hirsutism" group (see Diagram).

Fractionation of 17-Ketosteroids

The resting urines of selected patients were extracted and the 17-ketosteroids fractionated according to the method of Brooks (1958), who gave data on six normal females aged 21-30. For this group the excretion of androsterone plus etiocholanolone amounted to 4.7 ± 1.06 (S.D.) mg. per day. Three "hirsutism" patients excreted from 7.7 to 13.6 mg. per day, and two others 3.7 and 6.7 mg. per day respectively. Two Stein-Leventhal patients excreted 5.3 and 7.0 mg. and two "? Stein-Leventhal" patients 4.0 and 10.7 mg. per day. In spite of this elevation in some patients of all groups it will be seen from Table VI that the ratio of androsterone/etiocholanolone was within limits in all cases. Of the two Stein-Leventhal patients, in one the ratio was at the lower level of normal and in the other at the upper limit. The ratio 11-hydroxyandrosterone/11-hydroxy-etiocholanolone was increased in the two patients with adreno-genital syndrome and in one each of those with Stein-Leventhal syndrome and suspected Stein-Leventhal syndrome. It is possibly increased (3.6) in one of the "hirsutism" patients. The separated 17-ketosteroids were divided according to their chromatographic properties into two groups—a less-polar and a more-polar group (Brooks, 1958). The former may be of extra-adrenal origin in part—for example, from the testes in men—and the latter comprise the 11-oxygenated ketosteroids of adrenal origin. In six normal females Brooks found a ratio of less-polar/more-polar of 4.89 ± 0.95 (S.D.). The values for the Stein-Leventhal patients were well within this range (Table VI).

The excretion of dehydroepiandrosterone was increased in at least two of the "hirsutism" patients and in the two with adreno-genital syndrome. The data in Table VI for these two latter patients are taken from that of the case herein reported and from a pre-pubertal case recently examined by us.

Pregnanetriol Excretion

Urinary pregnanetriol has been determined by the method of Bongiovanni (1954), and in some instances confirmed by paper chromatographic separation. It is readily estimated and the importance of its estimation is considerable, for it is excreted in large amounts in the adreno-genital syndrome. It has been estimated in a group of cases, for the most part severely affected by hirsutism, where the possibility of the

TABLE VI.—Fractionated Resting 17-Ketosteroids

	No. of Subjects	Androsterone/Etiocholanolone	11-Hydroxyandrosterone/11-Hydroxyetiocholanolone	Dehydroepiandrosterone (mg. per day)	Less-polar/More-polar
Normal	6	1.31 ± 0.45 (S.D.)	2.37 ± 0.96	0.4 ± 0.36	4.85 ± 0.95
"Hirsutism"	5	0.8-1.8	2.1-3.6 (4)	0.7-1.7 (3) 2.2; 5.3 (2)	3.0-5.2 (5)
Stein-Leventhal syndrome ..	2	0.4; 2.1	1.9; 7.7	0.2; 0.5	3.6; 3.7 (2)
? Stein-Leventhal syndrome ..	2	1.1; 1.4	3.0; 4.7	0.2; 0.7	3.0; 6.2 (2)
Adreno-genital syndrome ..	2	1.0; 1.7	6.0; 5.0	3.6; 3.2	3.0; 2.0 (2)

presence of the adreno-genital syndrome arose. In all three groups the values in some cases, when given corticotrophin, were above the level of 5 mg. per day which is tentatively considered to be the upper limit of normal. It is striking that in one of the "hirsutism" patients a level of 16.4 mg. was reached (Table VII).

In considering the interpretation of high levels of pregnanetriol the following points are of importance. In the adreno-genital syndrome the metabolic block in steroid synthesis leads to a deficiency of corticoid synthesis (Dorfman, 1954) and hence of the corticoid metabolites in the urine, with a parallel increase of pregnanetriol and related substances. Therefore under these conditions the ratio of pregnanetriol/corticoid metabolites will be very high in comparison with the normal. If the ketogenic steroid method here employed is used for the determination of the corticoid metabolites, pregnanetriol is also included in the estimate. Since the chromogenicity of this substance after oxidation is approximately 1, an idea of the amount of the corticoid metabolites (sufficient for our purpose) can be

TABLE VII.—*Pregnanetriol Excretion (mg. per day)*

	Response to Corticotrophin		
	Resting Pregnanetriol	Pregnanetriol	17-Ketosteroids
"Hirsutism": 4 patients	0.8-1.8	2.4-4.8	31-52
3	1.1-2.7	7.6-16.4	36-74
Stein-Leventhal syndrome: 2 patients	1.7-1.8	4.4-5.6	16-40
2	1.4-2.6	6.9-10.3	27-37
? Stein-Leventhal syndrome: 2 patients	2.6 1.0-2.9	2.4-6.0	17-38

obtained by subtracting the value for pregnanetriol from the figure for ketogenic steroids. Under normal circumstances the ratio is 1/10, but we have found that in the adreno-genital syndrome the value for pregnanetriol can even exceed that for ketogenic steroids, giving an apparent ratio of infinity. On direct determination by chromatography the resting ratio pregnanetriol/tetrahydrocortisone in the case in Table VIII is 6/1. Under normal circumstances, from data given by Prunty (1956) and by de Courcy *et al.* (1953), it should be in the neighbourhood of 1/3. This finding is therefore in agreement with the above conclusion.

Returning now to the question of the high values observed for pregnanetriol in some of the "hirsutism" cases given corticotrophin (Table VII), determination of the ratio pregnanetriol/(ketogenic steroids - pregnanetriol) in response to corticotrophin shows the values to fall between 1/6 and 1/8, and for the Stein-Leventhal syndrome between 1/9 and 1/13. It is therefore justifiable to conclude that the production of corticoid metabolites was good in these cases in response to corticotrophin, and that the degree of any metabolic block, if present, is of a much lower order than in the true adreno-genital syndrome.

Adreno-genital Syndrome and Carcinoma of Adrenal Cortex

It has been stated that one of the series of 49 cases of hirsutism developing after puberty is considered to be a true example of the adreno-genital syndrome. The features of this case are given in Table VIII. Apart from these it was noted that the patient was short in stature and union of her bony epiphyses had occurred. The main features of her steroid pattern have been indicated above. The resting value for 17-ketosteroids and their response to corticotrophin, although elevated, lie within the limits of the patients with hirsutism. The raised value of the ratio 11-hydroxyandrosterone/11-hydroxyetiocholanolone (Table VI) conforms with the metabolic block in corticoid synthesis, and the elevation of dehydroepiandrosterone in many of these cases is well recognized (Broster *et al.*, 1953).

The patient with adrenal carcinoma has been included as an example of a further cause for development of post-pubertal hirsutism, and data for this patient are also given

TABLE VIII.—*Details of Case of Adreno-genital Syndrome and Case of Carcinoma of Adrenal Cortex*

	Case of Adreno-genital Syndrome	Case of Carcinoma of Adrenal Cortex
Age	18 years	21 years
Onset	14 ..	17 ..
Menses	Regular	Regular
Clitoris	Enlarged	Enlarged
Ovulation	+	
Ovary size	Normal	
Obesity	None	None
Acne	Moderate	Moderate
17-Ketosteroids	14.8-20.8 mg. per day	29.8 mg. per day (β fraction 1.2 mg.)
Ketogenic steroids	10.6-19.0	" "
Pregnanetriol	11.7	" "
Pregnanetriol/tetrahydrocortisone	6/1	
Response to corticotrophin:		
17-Ketosteroids	46 mg. per day	
Pregnanetriol	54	" "

in Table VIII. Here it is important to emphasize that elevation of the 17-ketosteroid level was not great enough to arouse high suspicion of the presence of carcinoma, and, as judged by assay of the β -ketonic 17-ketosteroid fraction, dehydroepiandrosterone excretion was not increased (data from Prunty, 1950; see also Dorfman and Shipley, 1956). By chance a definite pre-operative diagnosis of adrenal tumour was made possible by x-ray examination (Special Plate, Fig. 3); a small tumour with an accompanying calcified thrombus containing tumour cells was outlined above the left kidney simultaneously shown up by intravenous pyelography. The tumour, which weighed 23 g., was removed, but leaving some of the cells in the adrenal vein. Great improvement occurred in the patient's symptoms, and she is known to have survived longer than 10 years (Prunty, 1944).

The presence of enlargement of the clitoris in these two patients should be emphasized as indicating a greater degree of virilization than that occurring in the "hirsutism" group. It is true that one of the patients in this group (Table III) also had enlargement of the clitoris, but insufficient information was available at the time to establish whether she too had the adreno-genital syndrome; she showed a partial degree of improvement after subtotal adrenalectomy.

Gonadotrophin Excretion

Through the kindness of Dr. J. A. Loraine, of Edinburgh, quantitative estimations of the "total" gonadotrophin in the urine of two patients from each of the major groups has been made. The values reported in Table IX are expressed

TABLE IX.—*Gonadotrophin Excretion (H.M.G. units per day)*

	First Patient	Second Patient
"Hirsutism"	6	7
Stein-Leventhal syndrome	<10	6
? Stein-Leventhal syndrome	5	5

as units of the provisional standard H.M.G.-20A (1 unit equals 1 mg.). The method used was that of Loraine and Brown (see Loraine, 1958). All the values here reported are normal and do not differ from one another.

Discussions

From the clinical point of view the surprisingly high incidence of the Stein-Leventhal syndrome in the group of patients presenting with hirsutism is of special interest. The accompanying menstrual disturbance and sterility were important. Mental changes were much less frequent than in the other patients. The degree of ovarian enlargement in no case reached the dimensions given by Stein *et al.* (1949) as being commonly present. The importance of minimal ovarian enlargement must therefore be stressed.

Somewhat surprising was the normal menstruation of the patients with, respectively, adreno-genital syndrome and adrenal carcinoma; the former was also known to ovulate. The nature of the lesion in the adreno-genital case is of interest. The biochemical abnormality appeared to be that typical of the common pre-pubertal adreno-genital syndrome. However, menstruation, even with ovulation, is unusual in such patients when they reach puberty, and all the signs in our patients developed after puberty. It has been noted that the patient was short in stature, and this might possibly be the only indication that the adrenal condition could have been present before puberty. Recently Blizzard and Wilkins (1957) made brief mention of a case in which the condition apparently developed after puberty.

Many of the existing reports on hirsutism in the literature may be biased by the heterogeneity of clinical material and, in the case of observations on steroid metabolism, by the non-specificity of the methods used. In the present observations on steroid fractionation most of the necessary hydrolysis was performed by the use of glucuronidase (Brooks, 1958), so that artifact formation was minimized and specific chromatographic separation of the compounds was made. The levels of ketosteroids found agree with the elevation of values reported in some cases of hirsutism and with the majority of normal values in the Stein-Leventhal syndrome (Dorfman and Shipley, 1956; Jailer and Vande Weile, 1954). Ten of the 25 cases of hirsutism exceeded the normal range, both for resting 17-ketosteroids and in response to corticotrophin (see Diagram). This tendency for increased response to corticotrophin in 17-ketosteroid excretion is reflected in the low ratio ketogenic steroids/17-ketosteroids for the "hirsutism" group (Table V) previously reported by Prunty (1956), and has been commented on by Nabarro *et al.* (1958). It seems one indication that some alteration of adrenal androgen secretion might occur in these patients.

The ovarian secretion of an androgen such as testosterone, as suggested by Plate (1951), might be evidenced by changes in the ketosteroid fractions, although as testosterone itself, for instance, is a potent androgen the amounts secreted could perhaps be too small to affect the results very significantly. Administration of testosterone to human subjects has given widely varying results for the ratio of androstosterone/etiocholanolone (0.3–3.4), depending upon the conditions (Fukushima, Dobriner, and Gallagher, 1954; Fukushima, Bradlow, *et al.*, 1954; Rubin *et al.*, 1954), so that little may be deduced in this respect from these experiments. No definite abnormality has emerged from the present observations. The secretion of an androgen such as testosterone not metabolized to 11-oxygenated C₁₉ steroids should raise the ratio of less polar/more polar ketosteroids. This was not observed to occur in two patients with Stein-Leventhal syndrome. It has, however, been noted in two male patients studied by Brooks (1958), the values being 8.8 and 7.9 owing to an increased less-polar fraction. Calculation of the corresponding ratio from the data of Rubin *et al.* (1954) shows a similar ratio to ours for females, but there was no increase for males. The significance of changes in the ratio 11-hydroxyandrostosterone/11-hydroxyetiocholanolone has previously been discussed by Brooks (1958). Its increase is recognized in the adreno-genital syndrome and is to be expected. The significance of the rise in this ratio in the Stein-Leventhal and "Stein-Leventhal" patients requires further study.

The behaviour of pregnanetriol excretion in these patients resembled that of the "hirsutism" patients and not that of the adreno-genital syndrome. The results of the gonadotrophin assay do not lend support to the idea that there is a large increase of luteinizing-hormone production in the Stein-Leventhal syndrome. So far as they go the observations do not give support to the view that there is, by the methods used, a detectable increase of ovarian androgen in the Stein-Leventhal patients, but there are indications from the present work that alterations in adrenal secretion can also occur in this syndrome.

Summary

Clinical observations on a group of 49 women developing post-pubertal hirsutism indicate the importance of sterility and menstrual disturbance in the Stein-Leventhal syndrome. Ovarian enlargement may be minimal.

Further evidence for an increase in adrenal keto-steroid excretion in a large proportion of patients with hirsutism is presented, and the biochemical distinction of these cases from the adreno-genital syndrome discussed.

Limited observations have given no definite indication of increase of an ovarian androgen metabolized to 17-ketosteroids in the Stein-Leventhal syndrome, nor of any large increase of luteinizing-hormone production.

The somewhat unobtrusive occurrence of an adrenal cortical carcinoma as a cause of post-pubertal hirsutism and a probable instance of post-pubertal development of the adreno-genital syndrome are presented.

We are indebted to our colleagues in the Department of Obstetrics and Gynaecology, especially to the late Dr. K. Bowes, to Dr. J. W. McLaren, head of the Department of Radiology, and to Dr. R. G. Shorter, in the Department of Clinical Pathology, St. Thomas's Hospital, for their co-operation.

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The terms of reference of the Food Standards Committee have now been revised. The Committee was set up in 1947 to advise Ministers on regulations to control the composition of food for the protection of consumers. The revised terms of reference are as follows: "To advise the Secretary of State for Scotland, the Minister of Agriculture, Fisheries, and Food, the Minister of Health, and as respects Northern Ireland the Secretary of State for the Home Department, on the composition, description, labelling, and advertising of food, with particular reference to the exercise of the powers conferred on Ministers by Sections 4, 5, and 7 of the Food and Drugs Act, 1955, and the corresponding provisions in enactments relating to Scotland and Northern Ireland." The new terms of reference give the Committee more scope to consider and recommend on the control of food labelling and advertising; previously the Committee could deal with the labelling only of foods for which standards of composition were prescribed. Another change is that liquid milk is no longer excluded, but the Committee will not deal with any aspect of milk until the Committee on the Composition of Milk has reported.

F. T. G. PRUNTY, R. V. BROOKS, AND D. MATTINGLY: POST-PUBERTAL HIRSUTISM

FIG. 1.—Theca proliferation and luteinization at edge of cystic follicle in ovary removed from patient with Stein-Leventhal syndrome. ($\times 96$.)

FIG. 2A

FIG. 3.—Radiograph showing left adrenal cortical tumour with calcified thrombus in left adrenal vein (case in Table VIII). Outline of tumour and thrombus is indicated above renal pelvis in accompanying diagram.

FIG. 2B

FIG. 2.—Radiographs showing ovarian shadows after induction of pneumoperitoneum. A, normal; B, from case of Stein-Leventhal syndrome.

J. W. FARQUHAR *ET AL.*: FAMILIAL HAEMOPHAGOCYTIC RETICULOSIS

FIG. 1.—Biopsy of spleen showing phagocytes in sinuses containing numerous erythrocytes. ($\times 420$.)

FIG. 2.—Section of bone marrow showing phagocytes containing erythrocytes and occasional nucleated cells. ($\times 420$.)

FIG. 3.—Section of lymph node showing phagocytes containing erythrocytes and nucleated cells. ($\times 420$.)

FIG. 4.—Section of liver showing infiltration of portal tracts by histiocytes. ($\times 64$.)