BIOCHEMICAL FINDINGS IN HUMAN RETINITIS PIGMENTOSA WITH PARTICULAR RELATION TO VITAMIN A DEFICIENCY*

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ALTHOUGH the clinical features of human retinitis pigmentosa and its modes of inheritance are well-known, the paucity of information concerning any biochemical factor in the disease is such that we have virtually no knowledge of its aetiology.

The present investigation, although largely of a routine nature, was undertaken as a first step towards clearing up this obscurity. Owing to the rarity of the cases—and the difficulty of bringing patients up to hospital for examination, the inquiry has spread over a number of years. The results have shown how desirable and necessary it is to investigate young subjects at a time when the disease is developing—rather than the older advanced cases in whom it is stationary. It is usually the latter who come to the ophthalmologist for advice, and it is unfortunate that parents who are themselves affected are often unwilling to alarm their children—or to learn the truth concerning their condition—by allowing them to be examined at an early stage.

The pathological evidence already obtained from human cases of retinitis pigmentosa, and from the analogous hereditary diseases in animals, points to a primary degeneration of visual cells which is followed by pigmentary degeneration of the retina. Duke-Elder (1940) has suggested that these changes may be “the result of a common aetiological factor, rather than related to each other by cause and effect”, but in the analogous lesion in rats, at least, the pigment migration occurs only at a late stage and appears to be a secondary feature.

The degeneration of the neuro-epithelium was at first regarded as being a form of abiotrophy in man (Collins, 1919), in the rat (Bourne, Campbell, and Tansley, 1938), and in the red setter (Lucas, 1954; Parry, 1953). Recent evidence, gained from the study of the disease in rats, has now shown that the breakdown of the visual cells actually begins before the differentiation of the retina has been completed (Lucas, Attfield, and Davey, 1955). The breakdown is also preceded by a loss of retinal function, as shown by a diminution in the amount of retinal anaerobic glycolysis (Walters, 1959). There is also some evidence that aerobic glycolytic potential is lost before a decline in retinal respiration in the early stages of the degeneration (Graymore, 1960). This observation raises the question whether certain enzymes essential to glycolysis are lacking in the retina, or whether the blood stream is failing to supply necessary substances.

* Received for publication May 1, 1961.

In a wider sense it suggests that in man the degeneration of the retina may be caused by some metabolic factor after the manner of an inborn error of metabolism (Garrod, 1923). The presence or absence of some essential biochemical factor is an interesting speculation, in view of the fact that the disease occurs in two forms—one hereditary and the other not—which, apart from the familial history, are clinically indistinguishable. Garrod (1923) laid the foundations of biochemical genetics in his investigation of alkaptonuria, a disease characterized by the excretion of alkapton, an intermediate product of metabolism. Similarly galactosaemia (Kalckar, 1959) a hereditary disease familiar to ophthalmologists by reason of the associated cataract, has been ascribed to the absence or weakness (Kirkman and Bynum, 1959) of an enzyme in the chain of metabolism.

In a recent discussion of the biochemistry of human genetics Brenner (1959) explained the “one gene—one enzyme” hypothesis first put forward by Beadle (1945), *i.e.* that genes control the chemical properties of protein molecules—and can control the metabolic pathways of the cell by determining the structural specificity of a particular enzyme.

Thus, in the case of congenital night blindness, Kalmus (1959) suggested that there was a metabolic block at the point of conversion of vitamin A into retinene. He considered that “the difference between normal and night-blind people might be a difference in an enzyme transforming the vitamin A into retinene; or it might be due to the absence of an isomerase (which would convert vitamin A into a form utilizable by the retinene); or alternatively it might be a difference in the opsin affecting its affinity to the retinene”.

Apart from the common feature of night blindness, there is of course a great difference between congenital night blindness and retinitis pigmentosa. In the former, there is no ophthalmoscopic abnormality of the retina, although it is possible that the minute structure of the rods may be defective while the photopic visual field and the visual acuity remain good. There is no systemic deficiency of vitamin A as in nutritional night blindness and the night blindness is unaffected by massive doses of vitamin A.

In retinitis pigmentosa, on the other hand, night blindness in childhood is followed by retinal degeneration—with a varying amount of pigmentary change. Dark adaptation shows a marked decline and the shape of the curve indicates that not only the rods but also the cones are degenerating. The electroretinogram is poor or absent from an early date and this change precedes the progressive loss of the visual fields. Visual acuity, being essentially connected with cone function, often remains good until middle age. The observation made by Campbell and Gebertt (1955) that, in a small group of affected subjects, the concentration of vitamin A in the blood was very low (ranging from 56–90 I.U./100 ml.), suggests that a deficiency of vitamin A might be one of the contributing factors in the disease.

From experimental work in animals there is, in fact, an increasing amount of evidence that a deficiency of vitamin A not only causes night blindness,

but may also cause structural degeneration of the retina. Thus Tansley (1933, 1936) found a decline in rhodopsin in the retina of vitamin A deficient rats and dogs, which was followed by an alteration in structure of the outer segments of the rods. Johnson (1939, 1943) confirmed this degeneration in rats and traced its progress to the inner segments of the rods and through the nuclear layers. Similar changes have also been described in the monkey.

In the rat the degeneration has been correlated with biochemical and functional changes in the retina (Dowling and Wald, 1958). These authors found that, on being deprived of vitamin A, the rat steadily lost its store of substance from the liver, and that when the latter was empty the blood level fell precipitately. At this time there was a fall in the rhodopsin and an onset of night blindness as measured by the electroretinogram. The opsin content of the retina declined a few weeks later—when structural degeneration was apparent in the retina, and at a time when there were systemic signs of vitamin A deficiency. The final degeneration of the retina coincided with marked deterioration in the general condition of the animal.

The only other known instances of pigmentary degeneration of the retina are those which are said to arise from a *serious disturbance of liver or alimentary function*—either of which might be associated with vitamin A deficiency. This disturbance can be caused experimentally by ligation of the bile duct (Dolganoff, 1897; Majima, 1925). In man there are a few instances of its occurrence in cirrhosis and other hepatic disorders (Takahashi, 1925). A few rare cases have been reported of coeliac disease in infancy, followed by Friedrich's ataxia, pigmentary retinal degeneration, and acanthocytosis (Bassen and Kornzweig, 1950; Singer, Fisher, and Peilstein, 1952; Kornzweig and Bassen, 1957; Jampel and Falls, 1958). These cases all occurred in Jewish children, two being brother and sister, and in each case there was consanguinity of the parents. Singer and others (1952) suggested that the malformation of the rod cells might be due to a mutant recessive gene which would express itself only in individuals homozygous for this gene. The later findings of Jampel and Falls (1958) suggests that biochemical factors may also play a part in causing the histological abnormality of the red cells and possibly also of the retina and cerebral tissue.

The clinical features associated with retinitis pigmentosa are such that the possibility of an *endocrine factor* must also be borne in mind. The onset of retinal changes in adolescence suggests that either the sex hormones or the thyroid might be concerned. The former might determine the preponderance of the hereditary disease in men as compared with women, or might account for those cases in which the inheritance is sex-linked. In others, *i.e.* in cases of the adipose type, there is clinical evidence of an associated pituitary disorder as in the Laurence-Moon-Biedl syndrome.

The complexity of the problem is obvious but, since the hereditary and non-hereditary forms of the disease are clinically indistinguishable, there is every likelihood of a biochemical abnormality which is common to both

forms. This may, moreover, affect not only the retina but also other tissues of neural or ectodermal origin.

Present Investigations

Our series of patients, ranging in age from 9 to 65 years, came from a wide area centred in the Midlands and were under observation during the period 1947–1959, some for as long as 12 years. The family history of each was obtained as fully as possible, and some genealogical tables have been included in this report (see Table IV, below).

In those who had a familial history there was a preponderance of males (30:19), while in those with no familial history there were sixteen females and only twelve males. The adults showed the ophthalmoscopic changes typical of retinitis pigmentosa, but eight of the children were too young to have developed them.

The general health of the group was good. Two men (Cases 34 and 44) were of the obese hypopituitary type—one (Case 44) with polydactyly; two young sisters (Cases 75 and 76) were pituitary dwarfs, with under-development of secondary sexual features; and two young women (Cases 4 and 57) were deaf. One boy (Case 24) aged 15 was mentally retarded.

Two cases of congenital night blindness were also investigated for comparison.

Experimental Procedure

A routine analysis of the common constituents of the blood was carried out initially—together with tests of liver and thyroid function (Fig. 1).

FIG. 1.—Basal metabolic rates in retinitis pigmentosa, by age.

The urinary excretion of amino-acids was also investigated. The results are summarized in Table I (opposite) and are commented upon in the discussion.

The most notable divergence from normal values was found in the level of vitamin A and of carotenoids in the blood, and estimations were continued over a long

TABLE I
BIOCHEMICAL ANALYSIS

Test	No. of Subjects Tested	Analysis	Range of Results (per 100 ml.)	Comment
Serum	89	Total cholesterol	116-375 mg.	Slightly above normal in all subjects over age 20
	89	Cholesterol esters	13-100 mg.	Normal
	18	Sodium	310-336 mg.	Normal
	18	Potassium	14-19 mg.	
	33	Total protein	6.0-7.4 g.	
	32	Albumin	3.0-4.1 g.	
		Globulin	2.8-3.7 g.	
		γ -Globulin	0.6-1.4 g.	> 1.0 in 44 per cent.
	43	Proteins	Normal	By electrophoretic pattern
		Lipoproteins		
	7	Amino acids	Normal	By chromatography
	19	Red blood cells	Normal	Shape, colour, and fragility
Urine	71	Vitamin A	38-162 I.U.	Below normal mean in 91 per cent.
		Carotenoids	20-223 μ g.	Below normal mean in 70 per cent.
Liver Function	13	Amino-acid excretion		Slight excess in five cases of methionine, lysine, and arginine in chromatographic pattern
	60	Alkaline phosphatase test	4.6-11.6	Normal
Thyroid Function	65	Thymol turbidity	0.5- 3.4	> 2.0 in 17 per cent.
	24	Basal metabolic rate	- 32 to + 54	Above normal in 21 per cent. Subnormal in 16.5 per cent.
	5	Radioactive iodine uptake and excretion	Normal	Normal in all subjects

period in 71 subjects, of whom seventeen were under the age of 15. Blood samples were always taken in the fasting state.

In normal subjects, the level of these substances in the blood (according to Kimble, 1939) is unaffected by ordinary meals, but the mean values recorded by

various observers show that there is a variation over a period of years which must be attributable to the general level of nutrition in the population (Table II).

TABLE II
COMPARISON OF MEAN VALUES FOR BLOOD VITAMIN A AND CAROTENOIDS
IN NORMAL SUBJECTS

Author	Date	No. of Subjects	Vitamin A (I.U./100 ml.)	Carotenoids ($\mu\text{g.}/100\text{ ml.}$)
Kimble	1939	64	109	126
Yudkin	1941	23	113	120
Campbell and Tonks	1949	133	108	85
Medical Research Council	1949	83	128	100
Standard mean			114	108

Our own figures (Campbell and Tonks, 1949) are the lowest, having been obtained from subjects in the same areas as those in which the retinitis pigmentosa patients lived, but during a period of fat rationing. The figures available from the Medical Research Council survey (1949) are higher. We therefore adopted an arbitrary 'mean' of the figures available, *viz.* vitamin A 114 I.U./100 ml. and carotenoids 108 $\mu\text{g.}/100\text{ ml.}$

We found that the individual range was substantially the same in normal and affected persons; for the latter, vitamin A 38–162 I.U./100 ml. (as compared with 69–157) and carotenoids 20–223 $\mu\text{g.}/100\text{ ml.}$ (as compared with 20–199). Fig. 2, and Fig. 3 (opposite), show the percentage distribution of vitamin A and carotenoids respectively.

FIG. 2.—Percentage distribution of blood vitamin A.

Nevertheless, in retinitis pigmentosa patients, the individual level of vitamin A was below the normal mean in 91 per cent. of the adults and in all the children. For carotenoids also it was below the standard mean in 70 per cent. of all cases.

FIG. 3.—Percentage distribution of blood carotenoids.

Relative Levels of Vitamin A and Carotenoids.—These were found to be constant in any one person over a very long period; four examples are shown in Table III.

TABLE III
SUCCESSIVE VALUES* FOR BLOOD VITAMIN A AND CAROTENOIDS
IN FOUR INDIVIDUAL CASES, 1948-59

Case No.		Year											
		1948	1949	1950	1951	1952	1953	1954	1955	1956	1957	1958	1959
42	Vit. A						69			66	88	80	
	Car.						120			169	192	158	
15	Vit. A									77	56	65	57
	Car.									195	172	277	197
26	Vit. A	56	68	84			90	97	93		77	77	56
	Car.	52	45	48			37	74	33		37	33	36
41	Vit. A			86	70				60		96	97	55
	Car.			55	39				57		62	80	52

* The yearly values are the average of repeated estimations.

Out of 65 cases, 49 showed a persistently low level of both, while 21 showed a low level of vitamin A in association with a normal carotenoid level.

Effect of Heredity.—In the same group of 65 cases, 38 had a positive family history and 27 did not. No difference was found between them in the range, mean values, or individual distribution of the levels of vitamin A or of carotenoids in the blood.

Related Subjects.—Simultaneous estimations were made on a group of 42 subjects closely related to fifteen of the patients (Table IV, opposite). All but one of 26 relatives who were affected had a subnormal level of vitamin A and fourteen had a subnormal level of carotenoids. Twelve of the sixteen unaffected relatives also showed a subnormal level of vitamin A and/or carotenoids.

The low levels of both substances were particularly evident in Family No. 2 (Subjects 4–9) which had a strong familial history of the disease. Two of the children were very young, but one (Subject 8) showed retinitis punctata albescens. She was later (at the age of 14) shown to have no night blindness.

We were able to carry out successive tests on three children of this family (Subjects 6, 7, and 8) during the years 1944–46 (Table V). Their respective ages in November, 1945, were 11, 7, and 4 years. During this month an absorption test for vitamin A was also carried out on each of them, and it was found to be defective in Subject 7.

TABLE V
SUCCESSIVE TESTS IN FAMILY NO. 2 (SUBJECTS 6–8)

Test		Blood Vitamin A (I.U./100 ml.)			Blood Carotenoids (μ g./100 ml.)		
Subject No.		6	7	8*	6	7	8*
Affected		Yes	Yes	No	Yes	Yes	No
Sex		Male	Male	Female	Male	Male	Female
Date of Test	13.10.44	52	45	93	42	33	56
	20.4.45	43	42	53	63	59	77
	28.9.45	55	22	27	18	12	29
	†8.11.45 { Fasting after 4 hrs	34 209	30 86	34 256	42 46	28 28	44 49
	25.6.46	39	52	—	51	42	—
	13.9.46	32	18	25	39	46	58
	13.12.46	47	20	—	45	32	—
	6.12.57	106	127	—	27	30	—

† Absorption test for Vitamin A

* Retinitis punctata albescens

Twelve years later (December, 1957), some members of Family 2 were tested again. Subjects 6 and 7, previously tested, showed a rise in vitamin A but not in carotenoids, the values being 106/27 and 127/30 respectively. A third affected brother showed similar values (107/40), but a fourth unaffected brother showed a higher level (122/85) of both substances. An unaffected child aged 2½, sister of Subject 8, gave normal values (122/133).

TABLE IV
ESTIMATIONS ON 42 CLOSELY RELATED SUBJECTS IN 15 FAMILIES

FAMILY No.	RELATED SUBJECTS	SUBJECT No.	AFFECTED		UNAFFECTED	
			VIT. A	CAR.	VIT. A	CAR.
1		1			100	147
		2	66	127		
		3	69	120		
2		4			80	22
		5			72	28
		6	34	42		
		7	30	28		
		8			34	44 [age 4] ♦
		9			24	29 [age 2½]
		10			147	88
		11	96	69		
		12			100	140
3		12			67	95
		13				
		14 _w	44	79		
4		15	80	51		
		16	90	100		
		17			55	60 [age 11]
5		18	67	24		
		19	86	58		
		20	77	85		
		21			96	65
		22	100	52		
6		23			125	91
		24	70	81		
		25			134	53 ♦
7		26	102	111		
		27	88	100		
		28			81	102 [age 11]
8		29			80	102 [age 8]
		30	68	147		
		31	69	120		
9		32			127	117
		33	86	104		
		34	89	127		
		35	58	97		
10		36	50	125		
		37	96	90		
11		38			76	193 [age 9]
		39	113	45		
12		40	73	57		
		41	84	81		
13		42	67	108		

♦ Retinitis punctata albescens

♦ Frohlich's Syndrome

Vitamin A Absorption

(Table VI).—Further absorption tests were carried out on thirteen cases, all of whom (except case 8, who was a child) had advanced clinical signs of the disease with very poor dark adaptation and gross restriction of fields. Central visual acuity was still good, being 6/18 or 6/12 in Cases 5, 6, 7, 8, 11, 12, and 13. The child (Case 8) was the son of Case 7, and already showed pigmentary changes in the equatorial part of the retina; 3 years later it was possible to test his dark adaptation, which was found to be very poor.

TABLE VI
VITAMIN A ABSORPTION TESTS IN RETINITIS PIGMENTOSA

Case No.	Age (yrs)	Blood Vitamin A (I.U./100 ml.)				Blood Carotenoids (μg./100 ml.)				Test Dose
		(Fasting) 0	4	7	24 hrs	0	4	7	24 hrs	
1	24	59	288	212	58	118	94	77	86	72,000 I.U. as Prepalin
2	25	80	205	262	130	52	35	18	19	
3	21	102	584	400	125	111	110	110	66	
4	41	103	980	—	—	167	125	—	—	
5	48	92	199	227	142	29	31	24	14	
6	36	68	430	264	88	169	178	182	191	Vitamin A acetate 2,000 I.U./kg. body weight
7	27	68	860	295	90	147	140	180	167	
8	10	69	490	—	—	120	120	—	—	
9	26	71	935	627	138	153	60	133	96	
10	21	75	235	112	66	39	30	38	39	
11	50	85	335	—	—	40	40	—	—	
12	35	90	478	—	—	205	195	—	—	
13	36	73	638	—	—	97	97	—	—	

Case 3 was of the obese, hypopituitary type with polydactyly.

Cases 1 to 5 were tested with vitamin A given as 72,000 units Prepalin; 6 to 13 received pure vitamin A acetate, 2000 units/kg. body weight. The level of vitamin A in the blood should be at a maximum after 4 hrs—and is regarded as normal in this test if it then shows an increase to seven times the fasting value. By this standard the response in six (Cases 4, 7, 8, 9, and 13) was good, while in all the others it was poor, particularly in Cases 2, 5, 10, and 11, in whom the fasting values of carotenoids were also exceedingly low.

In none of these thirteen cases was there any increase in the level of carotenoids.

Biochemical Findings

There are no previous records of a systematic biochemical investigation of cases of retinitis pigmentosa, apart from the report made by Jampel and Falls (1958) on one of the rare cases of pigmentary retinal degeneration found in association with Friedrich's ataxia, subsequent to coeliac disease in infancy. In this case the β and γ -globulin and the blood cholesterol (total 37m./100 ml., esters 23, free cholesterol 14) were all extremely low, whereas there was no biochemical abnormality of urobilinogen, serum proteins, thymol turbidity,

glucose tolerance test, nor of the calcium, phosphorus, or bilirubin of the serum.

The red blood cells were crenated (acanthrocytosis) and showed an increase in saline fragility in all three cases, a condition which may have been due to the extremely low cholesterol. There was also slight normochromic and normocytic anaemia.

Blood Constituents.—In the retinitis pigmentosa subjects examined in the present survey there was no abnormality of the red blood cells. The sodium potassium, cholesterol esters, and proteins (including the electrophoretic pattern) of the serum were normal in amount and distribution. The total cholesterol was slightly above average in all subjects over the age of 20, while the γ -globulin showed a value of >1.0 in fourteen out of 32 subjects. The latter bore no relation to the increase in the thymol turbidity test found in eleven out of 65 subjects.

Liver Function.—There was no indication of a disturbed liver function as shown by the alkaline phosphatase test.

Amino Acids.—The amino-acid pattern of the blood in the few cases examined was also normal, and the increase in amino-acid excretion observed in five out of thirteen subjects cannot be regarded as significant without further investigation. This point is, however, of some interest, since Omayada (1957) Yamaji, Mirayi, Matsumoto, Muraji (1958), and other Japanese workers have reported that certain amino-acids, of which methionine is one, have a remarkable effect in augmenting the regeneration of visual purple, so that any increased loss of amino-acids might be of some significance in relation to retinal function.

Vitamin A and Carotenoids of the Blood.—By far the most interesting biochemical findings are those relating to the vitamin A and carotenoids in the blood.

Retinitis pigmentosa subjects appear to have a persistently low level of vitamin A in the blood—the mean value being well below that of normal subjects in 91 per cent. of the adults and in all affected children. It is frequently accompanied by a low level of carotenoids. These characteristics appear alike both in hereditary cases and in those with no family history.

These low levels of vitamin A and of carotenoids may persist in individual subjects over many years (Table III) and appear not only in affected but also in non-affected members of the same family (Table IV).

In normal healthy subjects a low level of blood vitamin A is usually the result of a prolonged deficiency of intake of vitamin A. The M.R.C. investigation of the human requirements of vitamin A (M.R.C., 1949) showed that, in a number of volunteers who submitted to a diet containing negligible amounts of vitamin A, the plasma value fell from a 'normal' level of 120 I.U./100 ml. to an average of 88 I.U./100 ml. within 2 months of deficiency.

Some of the subjects (ten out of sixteen) showed a further fall in 8 months, which in four cases reached a level of less than 50 I.U./100 ml.

In normal subjects the vitamin A plasma level has been found to be particularly low in an urban population and especially during a period of dietary restriction of butter and milk (Campbell and Tonks, 1949). There was, however, no indication of a deficient vitamin A intake in the diet of our retinitis pigmentosa subjects in the post-war years.

The result of the vitamin A absorption tests suggests that in quite a number of the affected subjects absorption is defective. Others have a ready absorption and their vitamin A responds to treatment with vitamin A or to a rise in the general level of nutrition—as in the case of certain members of Family 2 between the years 1945 and 1957.

The plasma level of carotenoids in retinitis pigmentosa remains characteristically high or low in each individual subject. In some it remains persistently low in spite of good nutrition. It is, of course, well known that in normal subjects the level of carotenoids in the blood is no criterion of the state of depletion of vitamin A but reflects the intake of carotene. Fat, which acts as a solvent, is necessary for the efficient absorption of carotene as well as of vitamin A from the gut. We have not yet tested the absorption of carotene in retinitis pigmentosa.

A possible alternative explanation is that the low level of carotenoids in the blood reflects their rapid utilization or conversion into vitamin A in the liver. If the body is short of vitamin A, it may draw heavily upon its carotenoids for conversion *via* retinine (Wald, 1953) into vitamin A, probably in the gut (Morton and Goodwin, 1956). According to Zechmeister (1949) and Dowling and Wald (1958), its pro-vitamin A activity depends upon its stereoisomeric form.

The constant finding of very low values of plasma vitamin A in affected children suggests that this is related to the early symptom of night blindness in retinitis pigmentosa. It is possible that it is also a factor in the structural degeneration of the retina. This idea is supported by the experimental production of retinal degeneration in animals by vitamin A deficiency, already referred to. The cases of acanthrocytosis and retinitis pigmentosa following coeliac disease described by Singer and others (1958) and Jampel and Falls (1958), although so rare, are possibly a link in this chain of evidence, since, from estimations carried out in our laboratory, we have found that there is an exceedingly low level of plasma vitamin A in coeliac disease. Moreover, in a case of steatorrhea associated with acanthrocytosis which was reported recently from the Children's Hospital, Birmingham (Salt, Wolff, Lloyd, Fosbrooke, Cameron, and Hubble, 1960), we found the plasma vitamin A to be only 19 I.U./100 ml. with a total absence of carotenoids and serum β -lipoprotein. On a gluten-free diet the vitamin A rose to only 31 I.U. but after several weeks on pure vitamin A it reached the level of 79 I.U. The carotenoids in the blood remained almost non-existent in the early weeks of

treatment. The child being only 18 months old was too young to show any ophthalmoscopic changes. Its subsequent progress, *i.e.* as to whether the retina and C.N.S. become affected—will be of considerable interest.

Thyroid Function.—It is well known that night blindness is found in association with hypothyroidism (Wohl and Feldman, 1939) and with a low level of vitamin A in the blood (Wendt, 1935).

In another direction we have been able to confirm that myxoedema is accompanied by diminished dark adaptation and a low level of blood vitamin A, with a very high level of blood carotenoids, while in the same cases the lipoprotein level is exceedingly high (Walton, 1960).

In retinitis pigmentosa there is no biochemical evidence of myxoedema, the thyroid activity as judged by the basal metabolic rate being normal in half of those tested. There was no individual relationship between the basal metabolic rate and the level of vitamin A or of carotenoids in the blood.

Those in whom the basal metabolic rate was found to be below normal were young subjects—several of whom were undersized for their years—while those with a raised basal metabolic rate were middle-aged subjects with advanced retinitis pigmentosa to whom the responsibility of their particular work was a considerable strain (Fig. 1) and might have given rise to an excess of thyroid activity.

Conclusion

The most significant finding is that of the persistently low level of vitamin A in the blood. In some cases this may be due to defective absorption, but there are several alternative considerations that require investigation, since either the transport mechanism or the storage of vitamin A in the liver may be defective. Again, the vitamin may circulate in a form which the retina cannot use, or there may be a metabolic defect in the retina itself in the early stages of the disease. It is not yet possible to form any opinion as to the cause of persistently low carotenoids in the blood of some of the patients.

We wish to thank the Ross Institute for the Prevention of Blindness for a grant which covered the expenses of patients coming for investigation. We are indebted to Dr. Blainey and Miss P. H. Vamplew of the Department of Experimental Pathology, University of Birmingham, for a chromatographic analysis of the urinary excretion of amino acids. We are also indebted to Dr. J. D. F. Williams, Physicist to the Coventry and Warwickshire Hospital for the estimations of the radioactive iodine uptake, and to Miss W. Robbins for secretarial help.

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