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A COMPARATIVE STUDY OF THE TOTAL CARBON DIOXIDE IN THE OCULAR FLUIDS, CEREBROSPINAL FLUID, AND PLASMA OF SOME MAMMALIAN SPECIES

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The distribution of chloride between the aqueous humour and plasma shows characteristic variations according to the mammalian species examined (Davson, Matchett & Roberts, 1952). Thus in the guinea-pig the concentrations in the two fluids are such that there is a deficiency of the ion in the aqueous humour, compared with the concentration in a plasma-dialysate, the value of the ratio: Concentration in aqueous humour/Concentration in plasma (R_{Aq}) being 0·935, compared with the value of 1·02 for the ratio: concentration in dialysate/concentration in plasma (R_{Dial}). In the horse, by contrast, the value of R_{Aq} is 1·14, indicating a large excess of chloride in the aqueous humour. In general, the variations in the distribution-ratio for the cerebrospinal fluid (R_{Csf}) are by no means so great, and in all the species examined there is an excess of chloride in this fluid (Davson, 1955): in consequence, the ocular and cerebrospinal fluids of the guinea-pig, for example, show a difference in chloride concentration of 21 %; in the horse, on the other hand, the ratios are very close, the difference being less than 4 %. The problem naturally arises as to whether the excesses of chloride are compensated by deficiencies of bicarbonate, and vice versa.

In the present study the bicarbonate distributions have been determined in a number of species. Characteristic variations have, indeed, been observed, and an attempt has been made to relate these variations with the buffering requirements of the intraocular contents; since the buffering capacity of the aqueous humour depends not only on its bicarbonate concentration, but also on its rate of renewal, the latter factor, measured by the rate of turnover of ^{24}Na, has been examined in a number of species. Wherever possible simultaneous studies have been carried out on the cerebrospinal fluid, as it is considered that points of distinction and similarity between these fluids are of importance in reaching a knowledge of their modes of formation, and of modifications they may have undergone to suit the tissues they bathe.

METHODS

Steady-state distributions: removal of the fluids. The animals used in this study varied so much in size that the same methods of sampling were not applicable to all species; the variations are described below. Usually the fluids were removed immediately after the induction of sodium pentobarbitone anaesthesia; when total CO_2 was to be determined the fluids were drawn into oiled syringes and kept under paraffin. The cerebrospinal fluid was in all cases removed from the cisterna magna. Adult animals were used throughout.

Albino rats. Arterial blood was obtained under paraffin oil from the tip of the tail in the unanaesthetized, heparinized animal; the samples were analysed separately. The animals were anaesthetized and the aqueous humour from six animals was withdrawn into the same syringe, and the pooled samples analysed. Pooled samples of cerebrospinal fluid were used, care being taken to obtain equal amounts from each animal.

Guinea-pigs. Blood was obtained by heart puncture; it was, however, not always possible to be certain that the left side of the heart had been entered. Aqueous humour and cerebrospinal fluid were taken as described in the rat.

Rabbits. Blood was taken from the main ear artery or, especially where repeated samples were needed, from the lateral ear vein. Analysis showed that the arterio-venous difference for total CO_2 was less than 1 m-mole/l. in the well-warmed ear.

Cats. Blood was obtained by heart puncture.

Dogs. Blood was obtained by femoral artery puncture.

Monkeys. *Cercopithecus aethiops* and *Erythrocebus pata* were used. Blood was obtained by heart puncture. The surprisingly high arterial total CO_2 in even very lightly anaesthetized animals was found to be 2–3 m-moles/l. lower than the total CO_2 of samples of venous blood from the well-warmed limb of an unanaesthetized animal.

Man. Aqueous humour was removed from the normal eye immediately before its enucleation on account of invasion of the orbit by an epithelioma. Blood was obtained from a vein in the warmed foot.

Goats. Blood was taken by heart puncture.

Horses. Blood was taken from a carotid loop or from the maxillary artery.

The vitreous body was aspirated with a wide bore hypodermic needle: with slight pressure on the eye the fluid entered the syringe easily. This method was used on the rabbit, dog and monkey. Vitreous body was also obtained from the enucleated and frozen eye (Davson & Duke Elder, 1948). This method allowed selected portions of the vitreous body to be dissected under paraffin and analysed separately. No significant difference was found whether the vitreous body was frozen in solid CO_2 or in liquid N_2; CO_2 was therefore used as it was more convenient to handle.

Determination of total CO_2. The fluids were analysed by the microdiffusion method described by Conway (1950) on 0·1 ml. samples.

Determination of pH. This was carried out with a Cambridge micro-glass electrode.

Determination of the rate-constant for turnover of ^{24}Na. The isotope was injected intraperitoneally into the unanaesthetized animal. At frequent intervals blood samples were withdrawn and finally, after 30 min, the animal was anaesthetized and the aqueous humour and the cerebrospinal fluid were withdrawn. Counts for radioactivity were determined with a 20th-Century Electronics liquid G.M. 6 counter, the usual corrections being made where necessary. The constant k_{out} was computed by a graphic integration.

RESULTS

For the rabbit, the distribution of total CO_2 between plasma and aqueous humour (R_{Aq}), plasma and cerebrospinal fluid (R_{Csf}), and plasma and vitreous body (R_{Vit}) was as follows, where R is the ratio: concentration in fluid/concentration in plasma-water:

R_{Aq}	R_{Vit}	R_{Csf}
1·28	0·97	0·94

The pH of the fluids were 7·48, 7·21 and 7·27 respectively. By application of the Henderson-Hasselbach equation, using values of 6·10 and 6·13 for the pK of plasma and the other fluids respectively (Shohl & Karelitz, 1926) one may compute the following values for the distributions of the bicarbonate ion between the fluids:

R_{Aq}	R_{Vit}	R_{Csf}
1·27	0·93	0·92

It is clear from these figures that no serious error will be introduced if, for convenience, the ratio of the total CO_2 concentrations is taken as equivalent to the ratio of the bicarbonate concentrations; in what follows this approximation will be made.

The values for the distribution ratios of a number of species are shown in Table 1; it is evident that there is a tendency for R_{Aq} to decrease with increasing size of the eye, i.e. for large eyes to exhibit a low concentration of bicarbonate by comparison with plasma, and vice versa. In Fig. 1 the values of R_{Aq} for both the chloride and bicarbonate ions have been plotted against the natural logarithms of the weight of the globe-contents; and it will be seen that, to some extent at any rate, there is a reciprocal relationship between the two distributions. Thus, the horizontal line represents approximately the Gibbs-Donnan distribution for univalent negative ions as determined from the distribution between plasma and its dialysate (Davson, 1955), so that points above the line indicate an excess of the ion in the aqueous humour over that in a dialysate, whilst points below indicate a deficiency. In the small-eyed guinea-pig the deficiency of chloride is associated with an excess of bicarbonate, whilst in the large-eyed horse the excess of chloride is associated with a deficiency of bicarbonate. If it is appreciated, however, that the concentration of bicarbonate in the plasma is only some quarter to a fifth that of the chloride ion, it becomes clear that this reciprocal relationship is not simply an expression of a tendency for the sum of the two concentrations to remain constant. For example, the actual excess of chloride in the horse's aqueous humour amounts to some 14 m-mole/l., whilst the deficiency of bicarbonate amounts to only 6·5 m-mole. Moreover, in the cat and dog there are actually excesses of both anions in the aqueous humour.

TABLE 1. Total carbon dioxide in the ocular fluids, cerebrospinal fluid and plasma expressed as m-moles/kg H_2O: and distribution of total carbon dioxide between aqueous humour and plasma (R_{Aq}), cerebrospinal fluid and plasma (R_{Csf}) and vitreous body and plasma (R_{Vit})

Species	Aqueous	Vitreous	Csf	Plasma	R_{Aq}	R_{Vit}	R_{Csf}
Horse	23·9 ± 3·3 (3)	—	26·9 ± 1·0 (3)	29·2 ± 2·0 (3)	0·82 ± 0·09 (3)	—	0·92 ± 0·09 (3)
Goat	21·8 ± 1·6 (2)	—	26·3 ± 1·9 (2)	32·9 ± 4·7 (2)	0·67 ± 0·04 (2)	—	0·81 ± 0·06 (2)
Dog	29·5 ± 2·6 (6)	25·1 ± 1·4 (4)	25·8 ± 2·2 (4)	26·2 ± 2·1 (6)	1·13 ± 0·07 (6)	0·91 ± 0·09 (4)	0·92 ± 0·05 (4)
Cat	31·0 ± 2·5 (8)	—	24·6 ± 1·8 (6)	25·1 ± 3·5 (6)	1·27 ± 0·09 (6)	—	0·95 ± 0·04 (5)
Monkey	28·9 ± 3·3 (6)	24·1 ± 3·4 (2)	28·9 ± 2·5 (6)	35·2 ± 3·4 (6)	0·77 ± 0·04 (6)	0·70 ± 0·01 (2)	0·78 ± 0·03 (6)
Rabbit	31·4 ± 2·4 (14)	26·2 ± 3·2 (8)	24·9 ± 2·5 (7)	24·9 ± 3·8 (14)	1·28 ± 0·09 (14)	0·97 ± 0·08 (6)	0·94 ± 0·04 (7)
Guinea-pig	40·0 ± 2·4 (6, 14)	—	26·6 ± 1·9 (4, 10)	29·8 ± 1·6 (6, 14)	1·35 ± 0·08 (6, 14)	—	0·91 ± 0·08 (4, 10)
Rat	33·8 ± 1·2 (2, 13)	—	29·2 ± 0·2 (2, 8)	30·0 ± 3·3 (13)	1·15 ± 0·03 (2, 13)	—	0·96 ± 0·04 (2, 8)
Man	26·3 (1)	—	—	28·4 (33·8)	0·93 (1)	—	—

Limits are standard errors. Numbers in parentheses are the number of animals used, except for the rat and the guinea-pig, where the first figure represents the number of experiments and the second the number of animals used. Figures for vitreous body and cerebrospinal fluid of the rabbit are derived from a later series than those for the plasma and aqueous humour; the average plasma concentration was 1·5 mM higher than in the earlier series. Values for R_{Aq}, etc., are the means of the individual values. The plasma obtained from the human subject was from venous blood with a concentration of 33·8 m-moles/kg H_2O: as this concentration is considerably higher than that normally found in arterial blood, the figure 28·4 m-moles/kg H_2O (Peters & van Slyke, 1931) has been used to compute the ratio.

A possible reason for the variations in the bicarbonate ratio may well be the different buffering requirements of the intraocular contents, a small eye requiring the secretion of a relatively concentrated bicarbonate solution to neutralize the stronger acids—lactic and pyruvic—formed by the lens and retina. If significant amounts of the bicarbonate in the freshly secreted aqueous humour were being destroyed by the stronger acids from the lens and retina, we should expect the concentration of bicarbonate in the vitreous body to be less than that in the aqueous humour withdrawn from the anterior chamber. As we have seen in the rabbit, the mean value of R_{Vit} is some 25% lower than the mean value of R_{Aq}. By sectioning the frozen eye at right angles to the antero-posterior axis, about 1 mm from the posterior pole of the lens, and analysing the two segments of vitreous body, the results shown in Table 2 were obtained, indicating that the anterior vitreous body has a concentration approximately equal to that of the aqueous humour, whilst the concentration in the posterior portion closer to the retina is considerably less.

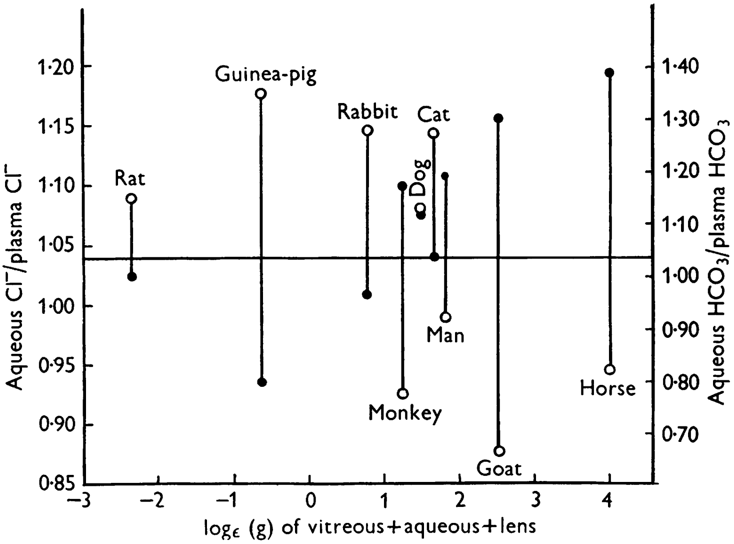

Fig. 1. Relationship of R_{Aq} for chloride and bicarbonate to weight (g) of intraocular contents. R_{Aq} for chloride in man is taken from Hodgson (1938) in other species from Davson *et al.* (1952). Weight of intraocular contents in man is computed by dividing total globe weight (v. Moellendorff, 1936) by the factor 1·13 which relates total eye weight to weight of intraocular contents in the cat and the dog. Open circles = HCO_3^- ratios. Closed circles = Cl^- ratios.

Rate of flow of aqueous humour. Since the amount of bicarbonate available to the intraocular contents is determined by the rate of flow of the aqueous humour, as well as by the bicarbonate concentration in the primary secretion by the ciliary body, it becomes of interest to find out whether there are any significant variations in the rate of flow amongst the different species. In the rabbit, it has been shown by Kinsey & Bárány (1949) that the rate of renewal of sodium in the aqueous humour measures, approximately, the rate of renewal of the aqueous humour as a whole. Thus the penetration of the isotope ^{24}Na from plasma into aqueous humour follows approximately an equation of the form

$$dC_{Aq}/dt = k_{In}C_{Pl} - k_{Out}C_{Aq},$$

where C_{Aq} and C_{Pl} are the activities of the aqueous humour and plasma respectively at any time, t. By measuring the changes in activity of the aqueous humour and plasma after an injection of ^{24}Na, k_{Out} may be computed; if the penetration and removal of ^{24}Na, into and from the aqueous humour, are determined entirely by secretory flow, then k_{Out} may be equated with the flow-constant, i.e. the fraction of the aqueous humour replaced in unit time. The results of measurements of this type are shown in Table 3; it will be seen that the values of k_{Out} for all species, except the rat, are included in the range 0·009–0·014 min^{-1}; the rat occupies an exceptional position with a value of k_{Out} equal to 0·024.

TABLE 2. Comparison of total CO_2 of the aqueous humour and of anterior and posterior portions of the vitreous humour in the rabbit. Results expressed as m-moles/kgH_2O

Aqueous humour	Vitreous body	
	Anterior	Posterior
33·7	32·4	26·6
30·0	31·1	27·0
30·8	30·4	25·1
32·2	32·5	25·0
34·1	34·7	27·3

TABLE 3. Value of the turnover-constant, k_{Out} (min^{-1}), for ^{24}Na in different species

Species	No. of experiments	Aqueous humour	Cerebrospinal fluid	References
Goat	1	0·0140	—	Present work
Dog	6	0·0135 ± 0·0005	0·00565 ± 0·0006	Present work
Monkey	3	0·0098 ± 0·0003	0·0057 ± 0·0017	Present work
Cat	6	0·014 ± 0·0005	—	Davson, Duke-Elder, Maurice, Ross & Woodin (1949)
Rabbit	75	0·0090	0·0041	Davson (1955)
Guinea-pig	5	0·0135 ± 0·001	0·0170 ± 0·0025	Present work
Rat	5	0·024 ± 0·005	0·019 ± 0·004	Present work

Results apply to experiments on unanaesthetized animals in all cases except the cat.

DISCUSSION

The main fact reported here, on which this discussion may be centred, is that there is a rough correlation between the size of the eye and the distribution of bicarbonate between its aqueous humour and the blood plasma. The correlation is by no means perfect, however, and any interpretation must account for the deviations from the general trend shown by the rat, monkey and man. It has been suggested earlier in this paper that the concentration of bicarbonate in the aqueous humour is an expression of the buffering needs of the ocular contents. The lens produces lactic acid, whilst the retina produces large quantities of pyruvic acid; in consequence the concentrations of these acids in the vitreous body are considerably greater than in the plasma (de Vincentiis, 1951; Auricchio & de Vincentiis, 1951). It may now be asked why a small eye should require relatively more bicarbonate than a large eye. In the first place, as Fig. 2 shows, small eyes are generally associated with lenses that are large by comparison with the total ocular contents, so that—other things being equal—a small eye would require a higher concentration of bicarbonate in its aqueous humour, to neutralize the stronger acids formed by the lens, than would a large eye. This consideration provides an immediate explanation for the anomalous position occupied by the eyes of monkey and man, in so far as the bicarbonate distributions in these species are closer to those of the large-eyed animals than to those of species having about the same eye-weight. It will be seen from Fig. 2 that the comparative size of the lens in monkey and man is remarkably small: so that, judged by the ratio of lens to globe-volume, these species belong to the large-eyed group of animals. A sufficient number of eyes has not been available from which to determine with any certainty the mean relative sizes of the lenses in the different species, but the approximate percentages of the volume of the globe contents occupied by the lens are as follows: man, 3·5; monkey, 4·5; horse, 8; goat, 9; dog, 10; cat, 15·5; rabbit, 16; guinea-pig, 20; and rat, 39.

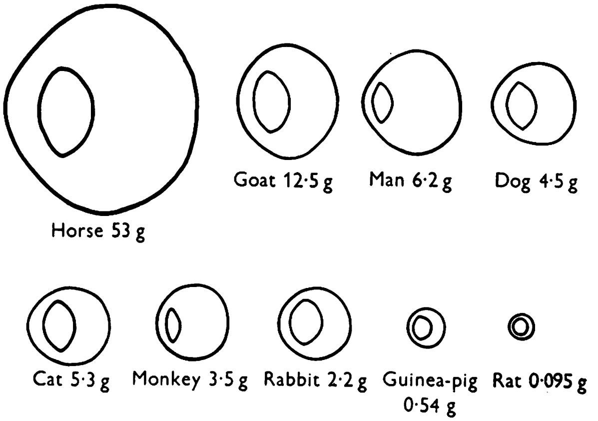

Fig. 2. Meridional sections of mammalian eyes, with weights of intraocular contents; the figure for the human eye is obtained by dividing total globe weight (v. Mollendorff, 1936) by the factor 1·13 which relates total eye weight to weight of intraocular content in the two species nearest in size. The human eye is drawn from Rochon-Duvigneaud (1943), the others from Davson (1953).

That the lens is not the only factor, however, will be clear when it is appreciated that the aqueous humour, withdrawn from the eye, is mainly derived from the anterior chamber, i.e. after the fluid has passed over the lens and presumably when the greater part of the neutralization of the strong acids formed by this body has taken place. If neutralization of the acids formed by the lens were the only factor of importance, we might expect that the aqueous humours would be secreted at varying concentrations in the different species, but that when the fluids were withdrawn from the anterior chambers the concentrations would be more or less the same. Actually, as we have seen, the concentration in the aqueous humour of one species may be some 30% higher than that in another. When we consider the retina, however, at some distance from the aqueous humour, the necessity for a high *gradient* of concentration across the intervening vitreous body becomes evident; the higher the concentration of bicarbonate in the freshly secreted aqueous humour, the steeper will be the gradient and the more efficient the diffusion to the site of production of the strong acids. Granted, therefore, the requirement of a gradient of concentration of bicarbonate from aqueous humour to retina, we must consider why a small eye requires a steeper gradient than a large eye. Here two factors may be operative. Small eyes are usually associated with small animals; the intensity of metabolic activity, expressed as rate of metabolism per unit weight of tissue, increases with the decreasing size of animal (an expression of the so-called 'surface-area law'). In the second place, since the ratio area/volume of a sphere increases as the radius decreases, the actual area of retina per unit volume of eye will increase with decreasing size of the eye. These two factors, together with the activity of the lens considered above, combine to give the general correlation between eye size and bicarbonate distribution. Support for the view that appreciable quantities of bicarbonate are destroyed within the eye is provided by the analyses of the vitreous body described earlier; and by the observation that poisoning of the retina with iodate likewise raises the concentration of bicarbonate in the vitreous body (Auricchio & Ambrosio, 1953).

Whilst the consideration of the lens/globe-volume ratio has permitted a plausible explanation for the anomalous positions occupied by man and the monkey, such a consideration cannot dispose of the remaining anomaly, namely the position of the rat: which has a bicarbonate distribution approximating to that of the dog, although its eye is the smallest of those considered here, and its lens/globe-volume ratio the highest. It will be recalled, however, that the rate of renewal of ^{24}Na in the rat is some two times greater than the average for all the other species examined; and it may well be that the buffering requirements of the rat's eye are met by a much more rapid turnover of the aqueous humour, instead of by an increased concentration of bicarbonate.

The cerebrospinal fluid differs markedly from the aqueous humour in showing much smaller variations in both the chloride (Davson, 1955) and bicarbonate distribution ratios; in general, the cerebrospinal fluid of all species approximates to the aqueous humour of the large-eyed animals, so far as these two distributions are concerned, exhibiting an excess of chloride and a deficiency of bicarbonate by comparison with plasma-dialysates. It is profitable, therefore, to regard the cerebrospinal fluid as the more generalized cavity-filling secretion; on this view, the aqueous humour may be considered to have undergone modifications in the various mammalian species—modifications that ensure an adequate buffering of the intraocular contents resulting in the maintenance of a pH in the vitreous body that is remarkably close to that of the cerebrospinal fluid. Since the vitreous body, like the latter fluid, is in close association with nervous tissue this becomes understandable. As to why the concentration of chloride in the aqueous humour should also be variable is a problem that awaits further investigation before a clear-cut explanation is possible.

It may well be, as suggested earlier (Davson, 1954), that the difference of osmotic pressure between plasma and aqueous humour is a variable factor amongst the mammalian species, and that this difference determines the rate of flow of aqueous humour consistent with a given intraocular pressure. If the differences of osmotic pressure are brought about by the secretion of variable amounts of chloride (accompanied, of course, by some cation) the variations in the chloride distributions are to be regarded as the sign of variations in osmotic pressure of the secreted fluids. In this event we should expect the cerebrospinal fluid to be hypertonic to the plasma and also, in those species showing a deficiency of chloride in the aqueous humour, hypertonic to the latter fluid. In the rabbit this is certainly true (Davson & Purvis, 1954).

Finally, two points relating the present findings to earlier work may be mentioned. Wang (1948) reported a value of 0·025 min^{-1} for k_{Out} for ^{24}Na in the dog; this is about twice the value found during the present work, and the discrepancy may be due to the circumstance that Wang worked on the anaesthetized animal. Another possibility is that he failed to separate the erythrocytes from the blood samples immediately; the dog's erythrocyte contains mainly sodium, and not potassium, so that unless the blood is centrifuged immediately after withdrawal the ^{24}Na in the plasma will continue to exchange with the inactive ^{24}Na in the cells; this will make the plasma activity lower than it actually was in the animal and lead to a fictitiously high value of k_{Out}. Secondly, it has been argued, from the observation that the concentration of bicarbonate in the aqueous humour of the rabbit is higher than in plasma, that the primary and fundamental step in the secretion of the aqueous humour is the active transport of this ion across the ciliary epithelium (Friedenwald, 1949). The observation of Becker (1954) that the carbonic-anhydrase inhibitor

Diamox lowers the intraocular pressure has, moreover, been taken as a confirmation of this theory. The present work, however, shows that a high concentration of bicarbonate is not by any means a general feature of the mammalian aqueous humour, so that it is unsafe to base a general theory as to the mechanism of formation of this fluid on a single feature of the chemical composition of the rabbit's aqueous humour. Moreover, the action of Diamox seems to be most pronounced in the human eye whose aqueous humour actually has a deficiency of bicarbonate; its action in lowering the intraocular pressure cannot, therefore, be taken as a confirmation of the theory.

SUMMARY

1. The total CO_2 content of the plasma, aqueous humour, vitreous body and the cerebrospinal fluid has been determined in several mammalian species.

2. The distribution ratio for total CO_2 between plasma and aqueous humour (R_{Aq}) shows marked species variation, the rat, guinea-pig, rabbit, cat and dog having an excess of total CO_2 in the aqueous humour, while the monkey, man, goat and horse have a deficiency.

3. R_{Aq} appears to be related to the mass of the intraocular contents and the relative size of the lens, the latter being probably the more important factor.

4. The distribution ratio for total CO_2 between plasma and cerebrospinal fluid (R_{Csf}) is below unity in all the species examined and shows no distinctive species variation.

5. The total CO_2 content of the vitreous body is lower than that of the aqueous humour in the three species examined, viz. rabbit, dog and monkey. In the rabbit the concentration of bicarbonate in the anterior part of the vitreous body is markedly higher than in the posterior.

6. The rate of turnover of the aqueous humour and cerebrospinal fluid, as estimated by the turnover-constant, k_{Out} for ^{24}Na, was determined in several species. The rat alone shows a distinctive species difference in turnover rate of the aqueous humour, with a higher rate than that of the other species. The guinea-pig and the rat have a significantly higher turnover rate of ^{24}Na in the cerebrospinal fluid than the other animals examined.

7. The pH of the plasma, aqueous humour, vitreous body and cerebrospinal fluid were determined in the rabbit and were: 7·46, 7·48, 7·21 and 7·27 respectively.

8. The species variation of R_{Aq} for bicarbonate is considered to reflect the varying buffering needs of the intraocular contents.

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