Serum Bilirubin during Exchange Transfusion The First Phase of the Rebound Phenomenon

By

J. Rosta

First Department of Paediatrics (Director: Prof. P. Gegesi Kiss), University Medical School, Budapest

(Received July 11, 1961)

It is generally recognized that exchange transfusion, performed in due time and with an adequate volume of blood, is the only reliable method of preventing the development of kernicterus in the newborn. Exchange of blood has the purpose to remove indirect bilirubin from the organism, and — in cases of blood-group incompatibilty — to rid the organism of the antibodies and of sensitized foetal erythrocytes, the sources of toxic pigments.

The efficiency of exchange transfusion depends, therefore, on the extent to which it helps in removing

(1) sensitized red corpuscles from the circulation, before their breakdown;

(2) accumulated indirect bilirubin from the organism.

The performance of the first task is easy because erythrocytes are confined to the intravascular compartment. The determination of circulating blood volume presents no difficulty. This is the reason why earlier workers — approaching the problem theoretically, by means of model experiments or in clinical practice — tried to express the efficiency of exchange transfusions by the mass of exchanged erythrocytes.

The performance of the second task is far more difficult. Extravasating, indirect bilirubin inundates the extravascular compartment, enters the cerebrospinal fluid and invades the tissues. The manner and extent of such distribution of the pigment are still largely a matter of speculation. We possess insufficient knowledge regarding the role played in this respect by the wall of the vessels, the cell membranes and the blood-cerebrospinal-fluid barrier. Neither do we know the further fate of the pigment in the tissue cells. We have but scanty data concerning the laws which govern the reflux of bilirubin into the bloodstream and the extent to which this process is influenced by the aforementioned factors.

It was with a view to obtaining answers to the many open questions in connection with bilirubin metabolism that we began to study the changes in bilirubin level during exchange transfusions. We propose to present a brief survey of the pertaining literature before giving an account of our results.

WASSERMANN et al. [14] were the first to demonstrate that, as regards red corpuscles, the efficiency of exchange transfusion can be represented by an exponential function. It expresses the ratio between the respective amounts of the original and the newly introduced erythrocytes. Employing the symbols used by ALLEN and DIAMOND, the formula is

$$R = \left(\frac{V - S}{V}\right)^n$$

where R = proportion of the infant's remaining erythrocytes
V = original blood volume of the baby in ml
S = single dose of exchanged blood, *i. e.* size of syringe in ml;
n = number of doses removed and replaced.

The results of theoretical computations were checked by means of experiments *in vitro* and serological tests. If red corpuscles labelled with radioactive phosphorus are placed in a closed compartment and the fluid therein exchanges by means of a syringe with the usual technique of exchange transfusions, activity will decrease according to the above formula [15]. The method of differential agglutination gives similar results for mixtures of erythrocytes of different serological properties.

The said experimentally verified formula used to serve for a long time as a guidance for determining the volume of blood to be exchanged. It was generally held that efficiency moved around 80 to 95 per cent if double the amount of circulating blood was exchanged [3, 4]. DOST [5], on the evidence of mathematical calculations concerning the efficiency of exchange transfusions performed with different methods, came to the conclusion that not more than 10 per cent of the original erythrocytes remained after 2 to 2.5 times the amount of circulating blood had been exchanged. He estimated the efficiency merely according to the exchanged mass of red corpuscles, and it was only in connection with freely moving antibodies that he mentioned their removal from the extravascular space as a possible further aim of blood exchange. It should be noted that the actual efficiency of an exchange transfusion is somewhat inferior to the theoretical one because that volume of blood which corresponds to the capacity of the cannula inserted in the umbilical vein is not exchanged but keeps streaming to and fro.

LATHE [10] was the first to focus attention to the fact that the decrease in the serum bilirubin level during the process of blood exchange remains behind the theoretical curve of erythrocyte exchange. Relying on the evidence of 10 cases of incompatibility and 10 cases of hyperbilirubinaemia, he stated moreover that the total volume of bilirubin removed in the course of exchange transfusion exceeded the amount of the originally circulating pigments. He explained this phenomenon with the reflux of pigment from the tissues during blood exchange.

KLEINHAUER and BETKE [9] studied in 6 cases the simultaneous changes in the level of serum bilirubin and in that of foetal haemoglobin in the course of blood exchange. The foetal haemoglobin is a good indicator of the amount of the remaining original red corpuscles, since its amount is 70 to 95 per cent in the erythrocytes of the newborn, while there is hardly 1 per cent in the blood of adult donors. The fall of bilirubin concentration was also in KLEINHAUER and BETKE's cases less than the decrease of the foetal haemoglobin level; it amounted to 90 to 95 per cent after the exchange of 400 to 600 ml of blood.

BROWN and ZUELZER [2] studied 7 cases with a similar method and presented the diagram of 5 exchange transfusions which likewise showed that the level of bilirubin decreased less than that of foetal haemoglobin. They recognized and stressed that exchange transfusion had to aim at the removal of both erythrocytes and bilirubin, and that the removal of the latter was the sole aim in cases of hyperbilirubinaemia. They studied the laws governing the outflow of the pigment from, and its reflux to, the blood path, and coined the term "rebound phenomenon" for the reflux; they explained the significance of this phenomenon in the repeated post-exchange elevations of the bilirubin level. 5 to 10-minute interruption of the process of blood exchange led to increases in the serum bilirubin concentration, and they drew the conclusion that slow and massive exchange transfusions were favourable for the removal of extravascular bilirubin.

FORFAR et al. [6] studied 45 cases of exchange transfusion with a view to observing the influence of volume and rate upon efficiency. While the significance of the quantity of bilirubin removed from the organism had been recognized by earlier authors as well, they were the first who regarded the amount of pigment removed from the circulation and the tissues as a criterion of efficiency. They found the intervention most efficaceous when the volume of exchanged blood amounted to 80 to 90 ml/lb (i. e. about 170 to 200 ml per kg). The most favourable rate appeared to be about 0.8 ml/lb/min. The exchange of more blood, although it may mean the removal of more pigment, is held by the said authors to be uneconomical. Again, a higher exchange rate than the said one leads to less efficiency and higher risks. It is worthy of note that, according to them, a slowing-down of the rate of exchange does not impair the efficiency of the intervention: no change in efficiency was observed even if the intervention lasted several hours after the rapid exchange of the first fraction of about 100 ml/kg.

MATERIAL AND METHOD

In the course of 1960 we studied, in connection with 30 exchange transfusions, the development of serum bilirubin concentration before the exchange and after the exchange of each 100 ml fraction of blood. The distribution of our material was as follows:

Nature of disorder:	No of cases:	No of exchange transfusions
Rh incompatibility	10	16
ABO incompatibility	4	5
Double incompatibility	2	3
Hyperbilirubinaemia	6	6

The mean weight of the infants was 2900 g: our material contained only 3 prematures with comparatively high body weights (2200 to 2300 g).

Details concerning our studies have been assembled in Table I. It shows the sex and birth weight of the infants, their and their mothers' blood group, the incompatibility (if any) between mother and child, and the result of Coombs' tests. Sensitization could not be demonstrated in three cases of Rh incompatibility and neither of the two cases of double incompatibility.

Table I shows moreover the time when the interventions began; the total amount of exchanged blood and its ratio to the weight of the infants: the blood group of donors. It is with a view to emphasizing the importance of the intervention being performed in due time that we indicate the precise age (in days and hours) of the infants at the beginning of the intervention. The rate of the transfusions is not indicated: it was 100 ml/15 min. throughout and did not, therefore, affect the evaluation of our results.

Further columns of Table I indicate the changes in serum bilirubin level during transfusion. Exchange transfusions were invariably performed through the umbilical vein, in fractions of 20 ml. The intervention began with the withdrawal of 20 ml of blood. The method of Gróf and Jendrassik [7] was used for bilirubin determination.

In the diagrams, the level of indirect bilirubin at the outset of the intervention is taken as 100 per cent, and all other figures refer to this value, while Table I indicates the percentual reduction of bilirubin concentration during blood exchange.

The last columns of Table I show the amount of bilirubin removed from the circulation and the tissues. The quantity of bilirubin removed from the blood paths was arrived at the following formula:

$$(B_1 \cdot P) - (B_2 \cdot P) \text{ where}$$

B_1 = level of bilirubin at the beginning of exchange transfusion
B_2 = level of bilirubin at the termination of exchange transfusion
P = amount of circulating plasma.

The volume of circulating blood was taken as amounting to 10 per cent, and that of circulating plasma to 5 per cent, of the body weight. (The mean haematocrit value amounts to 50 in the newborn.)

The determination of the amount removed from the organism means a more arduous task.

If we multiply the value for bilirubin at the end of transfusion by the amount of removed plasma we obtain „the minimum mass of bilirubin withdrawn" from the organism (Forfar, [6]). The true figure will obviously exceed this value. We can obtain the real value if we determine the amount of removed pigment in each single fraction of exchanged blood or if we mix all fractions with heparin and establish the concentration of bilirubin in the mixture.

These procedures are laborious, and so we tried to arrive at the real value by mathematical means. We were helped in this by the curve illustrating the drop of the pigment level during 30 exchange transfusions. By dividing the exchange of 100 ml of blood, computing the mean bilirubin concentration at the beginning and at the end of each section, and by multiplying this value with the amount of plasma withdrawn in the given section (always 50 with our present method), we obtain the approximative quantity of removed bilirubin in respect of that section. Adding up all these sectional values we arrive at the approximative

total value of bilirubin withdrawn during the entire procedure:

$$B = S\left(\frac{a1 + a2}{2} + \frac{a2 + a3}{2} + \ldots\ldots + \frac{an - 1 + an}{2}\right) =$$

$$= S\left(\frac{a1}{2} + a2 + a3 + \ldots\ldots + \frac{an}{2}\right) \text{ where}$$

B = amount of bilirubin withdrawn
S = amount of plasma withdrawn between two measurements (i.e. 50 in our cases)
$a1$, $a2$, an = bilirubin level for each corresponding 100 ml fraction of exchanged blood.

Table I indicates both the minimum and the "real", i. e. approximative total mass of withdrawn bilirubin. A comparison of the two columns will make it evident that the real value of removed pigment was far in excess of that resulting from the usual computations.

Results

Fig. 1 shows the decrease in bilirubin level in 30 exchange transfusions. The similarity of the curves is well perceptible notwithstanding the scatter of values.

Fig. 2 shows the mean values in respect of transfusions made in different groups (Coombs' positive, Coombs' negative incompatibility; hyperbilirubinaemia; repeated ex-

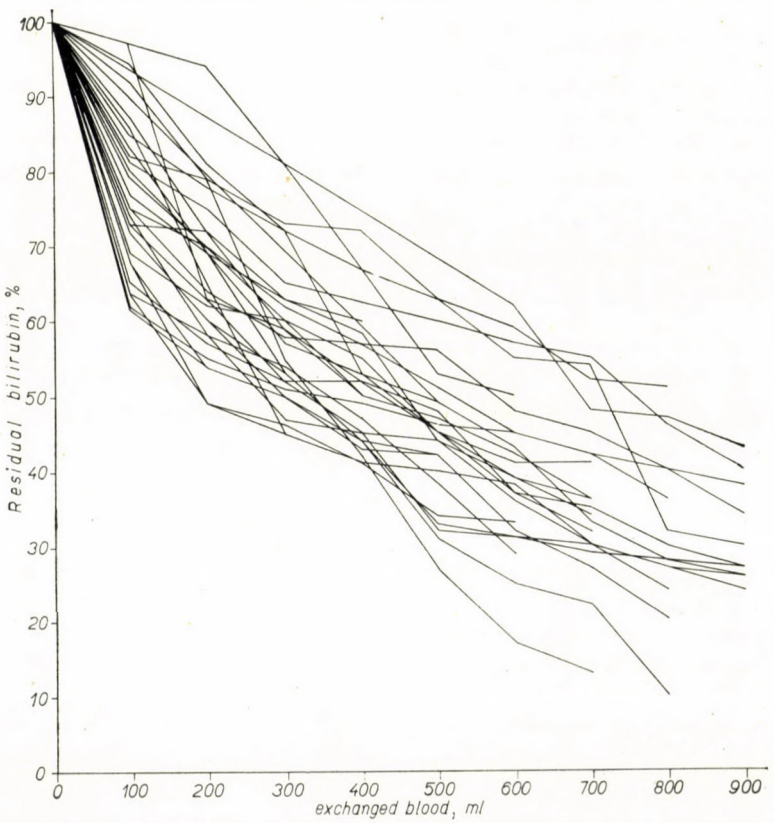

Fig. 1

TABLE I

Case No.	Name	Sex	Birth weight	Blood group of			Coombs	Blood exchange			Group
				Infant	Mother	Incom-patibilty		Time (day/hr)	Volume	ml/kg	
1.	G. K.	♀	3150	B+	AB—	Rh	+	1, 21	900	285	B—
2.	B. R.	♀	2800	AB+	B+	∅	—	8,	350	125	AB+
3.	K. E.	♀	3400	O+	O+	∅	—	5, 16	900	265	O+
4.	P. Zs. II.	♀	2900	A+	O+	AO	—	7,	600	206	A+
5.	K. G.	♀	2650	A+	O+	AO	—	3, 11	300	115	A—
6.	M. J.	♀	3000	A+	A—	Rh	+	0, 10	900	300	A—
7.	II.							3, 1	900	300	A—
8.	P. A.	♀	2900	A—	A+	∅	—	5, 18	700	240	A—
9.	R. S. II.	♂	3100	A+	A—	Rh	+	2, 6	900	290	A—
10.	Sz. Z.	♂	3000	A+	O—	Rh AO	—	2, 3	900	300	A—
11.	V. R.	♀	3200	B+	O+	BO	—	1, 7	950	296	B+
12.	C. Á.	♀	2250	B+	B+	∅	—	5, 14	800	360	B+
13.	M. I.	♂	2300	B+	AB—	Rh	—	4, 13	700	304	B—
14.	Sz. É.	♀	3500	B+	O—	Rh	—	2, 14	900	257	B+
15.	II.							4,	600	172	B—
16.	G. K.	♀	3300	O+	A—	Rh	+	3, 5	900	272	O—
17.	II.							4, 2	600	181	O—
18.	G. É.	♀	3050	O+	O—	Rh	+	, 12	900	295	O—
19.	II.							1, 12	900	295	O—
20.	III.							2, 12	700	233	O—
21.	L. M.	♀	3000	O+	O—	Rh;	+	1, 23	900	300	O—
22.	Sz. Zs.	♀	3400	B+	O—	Rh BO	—	2, 5	700	205	B—
23.	II.							4, 5	700	205	O—
24.	B. A.	♂	3200	B+	A+	∅	—	3, 7	800	250	B+
25.	L. J.	♀	2400	A+	O+	AO	—	2, 21	700	293	A—
26.	II.							5, 21	800	333	A—
27.	P. J.	♂	2600	A+	AB—	Rh	—	2, 13	500	191	A—
28.	A. J.	♂	2200	A+	A+	∅	—	6, 7	400	182	A—
29.	H. N.	♀	2540	A+	A—	Rh	+	0, 12	720	288	A—
30.	II.							1, 14	800	320	A—

+ up to the last values of the series.

Before transf.	Serum bilirubin level after the exchange of (ml of blood)									% Decrease	Mass of removed bilirubin		
	100	200	300	400	500	600	700	800	900		from circulation	from organism	
												minimal	real
18.3	11.4	10.1	9.3	8.2	6.2	5.8	5.5	5.1	4.5	76	21.73	20.25	36.50
22.0	19.0	14.4	10.0							45	16.80	15.00	24.70
24.0	22.1	19.0	17.6	17.4	15.2	13.2	13.0	7.6	7.2	70	28.56	32.40	70.35
23.4	22.8	22.1	19.0	15.8	9.3	9.0				62	20.88	27.00	52.60
21.0	14.3	11.4	10.5							50	12.72	17.10	20.75
14.2	—	—	10,2	—	—	7.8	6.0	5.9	5.4	67	13.20	24.30	41.20
22.5	21.4	14.0	11.4	11.4	10.1	8.2	7.8	6.0	6.8	73	23.25	27.00	53.67
22.1	16.2	16.1	13.1	11.4	10.7	8.3	7.3			68	21.46	25.55	45.25
29.3	22.2	18.9	17.2	17.0	16.5	14.2	13.3	11.9	10.5	66	28.83	47.25	75.35
19.0	15.8	13.2	12.0	12.0	10.8	8.4	6.9	5.7	5.0	74	21.00	22.50	48.40
14.2	—	—	—	8.4	7.0	6.1	4.7	4.0	3.9	76	16.48	17.55	33.12
24.2	17.5	14.7	12.3	10.5	10.4	8.1	6.7	4.8		80	21.82	19.20	47.35
30.0	23.7	21.0	18.2	16.7	13.7	12.4	12.4			59	20.24	43.40	63.75
30.4	19.6	17.2	15.8	13.6	9.8	9.5	8.8	8.6	7.8	74	39.55	35.10	61.00
22.1	15.2	10.9	10.1	9.1	7.5	7.3				67	25.90	21.90	33.75
32.0	23.4	20.2	19.0	16.0	15.2	13.6	11.7	9.2	—	64+	37.62	41.40	69.85
26.6	20.2	18.0	15.0	14.0	12.8	10.7				57	26.34	32.10	49.32
22.6	18.6	17.2	15.0	—	13.8	13.1	12.9	11.5	10.0	60	16.21	45.00	66.40
25.1	15.7	13.8	12.9	12.2	11.5	11.2	10.5	10.0	9.6	62	23.63	38.40	57.55
29.0	23.5	20.0	15.4	12.8	12.4	—	—			58+	25.31	43.40	46.20
16.0	12.0	10.6	10.0	9.2	8.8	8.0	7.2	6.8	5.8	74	15.30	26.10	41.75
19.2	12.5	11.2	9.2	8.8	8.6	7.6	7.1			64	20.57	24.85	35.52
26.5	21.8	21.0	14.7	11.5	7.3	4.5	3.5			87	39.10	12.25	47.90
19.2	12.5	9.5	9.0	4.8	7.9	6.9	6.7	5.9		76	21.28	23.60	34.92
22.3	16.7	13.0	12.1	10.6	8.6	6.5				71	16.36	22.75	37.70
20.0	14.4	12.0	10.6	8.8	6.2	5.0	4.5	2.0		90	21.60	8.00	36.25
14.6	12.7	10.6	9.2	8.8	—					38+	7.54	22.00	22.10
25.3	17.7	15.8	15.4	12.8						50	13.75	25.60	33.97
19.0	17.2	15.0	13.8	10.2	8.6	7.4	6.6			66	15.87	23.76	42.50
23.7	22.5	19.2	17.3	15.9	15.0	14.0	12.5	12.2		49	14.72	48.80	67.17

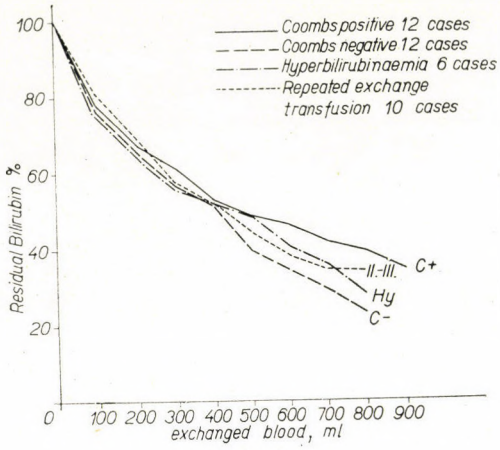

FIG. 2

changes). Certain cases of blood exchange have been included twice (e. g. a second exchange on account of Rh incompatibility), and so Fig. 2 contains a total of 40 observations (the four groups are composed of 12, 12, 6 and 10 cases, respectively). It is seen that the curves run practically similar courses. The slower decrease of pigment concentration in the Coombs positive group during the second phase of exchange may have been due to haemolysis, a phenomenon which was most pronounced in this group.

The curve representing the mean values for all our 30 cases is shown in Fig. 3 together with the curve representing the exponential function which expresses the theoretical value of the exchange of red corpuscles. It can be seen that the first curve is considerably less steep than the second, a phenomenon due to "rebound", *i. e.* the reflux of bilirubin from the extravascular space into the circulation. The curve in the lower

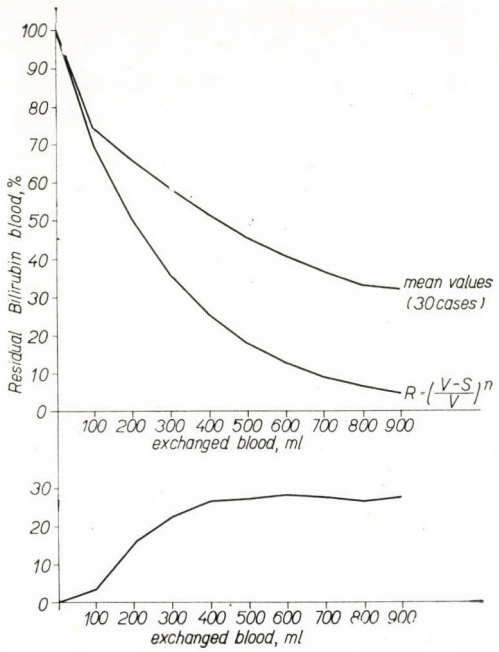

FIG. 3

part of Fig. 3 shows the extent to which the rebound phenomenon impeded the reduction of pigment concentration. Rebound, *i. e.* reflux, was increasing during the first phase of transfusion which, in our cases,

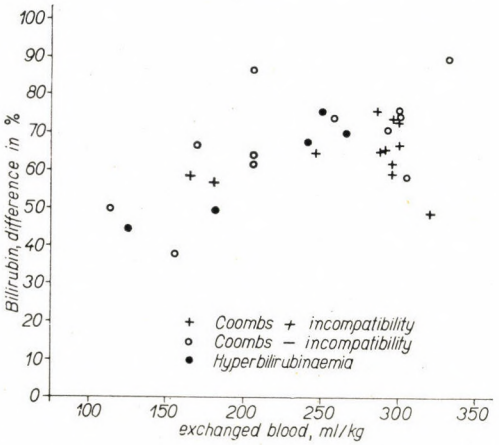

FIG. 4

meant the exchange of 1.5 times the circulating blood. It remained stationary during the second phase when the exchanged amount had reached the threefold of circulating blood. This would mean that, in the second phase, approximatively the same amount of bilirubin streamed back to the circulation as had been removed therefrom.

Fig. 4 shows the correlation between the volume of exchanged blood and the decrease in bilirubin concentration during the intervention. It can be seen that — within the given limits — an increase in the volume of exchanged blood went hand in hand with the decrease in the concentration of bilirubin.

Fig. 5 illustrates the relationship between the volume of exchanged blood and the mass of pigment which — according to our calculations — had actually been removed from the organism. Although an increase in the exchanged amount of blood generally meant an increased amount of removed pigment, the varying efficiency of transfusions with and above 300 ml/kg is a phenomenon that requires further investigations.

Discussion and Conclusions

It has been pointed out at the beginning that the chief purpose of exchange transfusion is the removal of bilirubin from the organism. It is for this reason that this study does not deal with the removal of red corpuscles, a subject which has been elaborated amply both theoretically and experimentally.

We have likewise pointed out that it is not easy to ascertain the possibilities of bilirubin removal. Reliable conclusions in this respect can be reached only if one knows the exact amount of indirect bilirubin accumu-

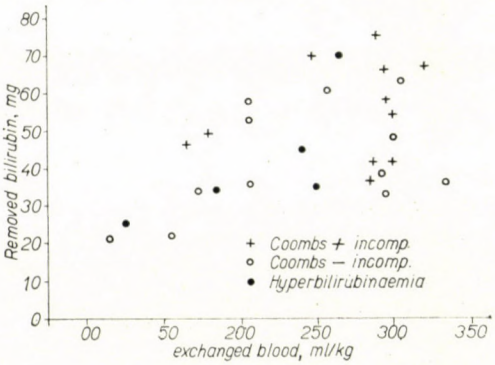

Fig. 5

lated in the entire neonatal organism at any given moment. However, all we are at present able to determine more or less exactly, is the amount of bilirubin in the blood vessels, while we have to resort to estimates as regards the bilirubin contained in the intracellular space. Its amount may be accepted about the eightfold of that circulating in the bloodpaths, since the ratio between the volume of plasma and the capacity of the intercellular space is about 1:8 in newborn infants (Kerpel-Fronius). Direct evidence regarding bilirubin level and contents of this space is still lacking.

There are some data that all kinds of neonatal jaundice, including physiological jaundice, lead to an increase

in the amount of bilirubin level in the cerebrospinal fluid [13]. There is, however, no linear relation between the bilirubin level of the serum and that of the cerebrospinal fluid. A more pronounced correlation exists between the respective cerebrospinal levels of protein and bilirubin. Indirect bilirubin in both the intra- and extravascular compartments is bound to albumin, and each g of albumin was found to be capable of binding 15 mg of bilirubin. It is, therefore, safe to assume that albumin plays a significant role in the distribution of bilirubin and even influences the permeability of the blood-cerebrospinal fluid barrier to pigments [12]. The parallelism between albumin contents and bilirubin level admits, thus, of conclusions concerning the amount of extravascular pigment with the proviso only that conditions in respect of proteins are the same in both regions of the body.

Even less is known concerning the amount of bilirubin accumulated in the tissues. All we know is that fat tissue, the brain and the intima of vessels bind bilirubin comparatively more rapidly and less reversibly than the other tissues. This is one of the aetiological factors of hyperbilirubinaemia in the premature infant. It should be noted in connection with the pigment metabolism of tissues that apart from the backflow into the extracellular space the breakdown of bilirubin, too, may have to be reckoned with. It must be borne in mind, further, that in the case of jaundice due to incompatibility a great number of erythroblasts and sensitized erythrocytes may disintegrate not only in the blood paths but also in the blood depots and at the sites of extramedullary haemopoiesis — all of them further sources of indirect bilirubin. It is chiefly in animal experiments that these as yet obscure aspects of bilirubin metabolism will have to be studied, since even the routine withdrawal of cerebrospinal fluid from human newborns would involve unnecessary risks. We have to content ourselves at present with clinical observations and the available methods in estimating the efficiency of exchange transfusions.

The result of our experiments justify the following statements:

(1) The decrease of the bilirubin level during an exchange transfusion remains behind the extent of erythrocyte exchange. This is due to the rebound phenomenon. Retarded erythrocyte exchange is most pronounced in cases of Coombs positive incompatibility. It seems to follow that haemolysis, continuing during exchange transfusion, may impair the efficiency of the intervention, to some extent at least.

(2) The intensity of the rebound phenomenon was found to increase in the first phase of transfusion, during which 150 per cent of the originally circulating blood volume were exchanged. The balance between the reflux and removal of bilirubin remained stationary in the second phase, during which another 150 per cent of the originally circulating blood volume were exchanged. It may be

concluded that transfusions with a threefold blood exchange promise the best results for the utilization of the rebound phenomenon, *i.e.* the removal of bilirubin.

(3) The observation that increasing the volume of exchanged blood brings about a pronounced decrease in the bilirubin level is a further argument in favour of an exchange three times the original volume of circulating blood.

(4) Mathematical computations have led us to agree with the reports according to which the actual amount of bilirubin removed from the organism by way of exchange transfusion is considerably in excess of the amount of pigment contained in the circulating blood at the beginning of transfusion, provided the volume of exchanged blood is sufficient. This has always been regarded as the most convincing proof of the rebound phenomenon. The real value of removed bilirubin, as determined in our experiments, shows that considerable amounts of the pigment may accumulate in the neonatal organism.

(5) A correlation has been found to exist between the increase in the volume of exchanged blood and the amount of removed bilirubin; yet, in some instances, the exchange of three times the circulating blood did not yield as favourable results as could have been expected on the evidence of other comparisons. This may have been due to unknown factors which affect the metabolism of bilirubin and become particularly operative in such cases because the said correlation seems to be most complex at this stage.

(6) Numerous authors have tried to ascertain whether it was by a single substantial exchange of blood or by two less substantial exchanges, made with a short interval, that more bilirubin could be removed [8]. Since we did not repeat the transfusion within 6 hours, we are not in a position to express an opinion on this subject. Observations of post-exchange "rebound" are now in progress which might supply further data concerning the problem.

(7) According to our clinical observations and experiments, exchange of three times the original circulating blood volume has to be carried out for the treatment of icterus gravis in the newborn. The incidence of complications is minimal if the exchange is performed with adequate care and rapidity (we observed complication but in a single instance in the course of the present series, and it occurred during the first phase of the exchange).

Summary

Changes in the serum bilirubin level were studied during 30 exchange transfusions performed on newborn infants. Owing to the rebound phenomenon, the decrease in the concentration of bilirubin remained behind the extent of erythrocyte exchange. This lag was most pronounced in

Coombs positive cases of Rh incompatibility. Exchange of three times the volume of circulating blood seemed to warrant the best utilization of the rebound phenomenon and so the most radical purification of the organism from indirect bilirubin. An attempt has been made to determine the true amount of bilirubin removed by the exchange transfusion. Its result is a further argument in favour of threefold exchange.

The author is indepted to Drs. I. Hittner, J. Szabó and M. Kocsis for the surgical interventions and to Mr. J. Nagy and Mrs. D. Szilágyi for technical assistance.

References

1. Allen, J. F., Diamond, L.: Erythroblastosis Fetalis. New Engl. J. Med. **257,** 659, 705, 761 (1957).
2. Brown, A. K., Zuelzer, W. W.: Studies in Hyperbilirubinemia. Amer. J. Dis. Child. **93,** 263, 274 (1957).
3. David, G., Boreau, Th., Ingrand, F., Maigret, P.: L'ictère de la Maladie Hémolytique du Nouveau-né. XVII[e] Congrès des Pédiatres de Langue Française, Montpellier. 1959.
4. Diamand, L. K., Allen, F. H., Thomas, W. O.: Erythroblastosis Fetalis VII. Treatment with Exchange Transfusion. New Engl. J. Med. **244,** 39 (1951).
5. Dost, F. H.: Der Blutspiegel. G. Thieme, Leipzig, 1953.
6. Forfar, J. O., Keay, A. J., Elliot, W. D.: Exchange Transfusion in Neonatal Hyperbilirubinaemia. Lancet **2,** 1131 (1958).
7. Jendrassik, L., Gróf, P.: Vereinfachte photometrische Methode zur Bestimmung des Blutbilirubins. Biochem. Z. **297,** 81 (1938).
8. Keuth, U., Partener, A.: Untersuchungen über den Wiederanstieg des Serumbilirubins nach der Austauschtransfusion sowie zur Frage des optimalen Intervalls bei unterteilter Austauschtransfusion. Z. Kinderheilk. **83,** 195 (1959).
9. Kleinhauer, E., Betke, K.: Die Kontrolle der Wirksamkeit einer Austausch-Transfusion bei Neugeborener. Ärztl. Wschr. **11,** 798 (1956).
10. Lathe, G. H.: Exchange Transfusion as a Means of Removing Bilirubin in Haemolytic Disease of the Newborn. Brit. Med. J. **1,** 192 (1955).
11. Lukács, V. F., Romhányi, J.: Az újszülöttkori vércsoport-inkompatibilitások kapcsán szerzett tapasztalataink. Gyermekgyógyászat **11,** 65 (1960).
12. Odell, G. B.: The Dissociation of Bilirubin from Albumin and its Clinical Implications. J. Pediat. **55,** 268 (1959).
13. Stempfel, R., Zetterström: Cerebrospinal Fluid Bilirubin in the Neonatal Period with Special Reference to the Development of Kernicterus. Acta paediat. (Upsala) **43,** 582 (1954).
14. Wassermann, L. R., Sharney, M. A.: Blood Exchange in Replacement Transfusions. I. Blood **5,** 925 (1950).
15. Wassermann, L. P., Rashkoff, I. A., Sharney, L., Yoh, T. F., Leavitt, D.: Blood Exchange in Replacement Transfusions. II. Blood **5,** 938 (1950).

Dr. J. Rosta
Bókay J. u. 53.
Budapest VIII., Hungary