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CHANGES IN CHLORIDE METABOLISM IN ACUTE FEBRILE DISEASES

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Examination of the urine has always been considered very important in acute febrile illness because of its striking changes in quantity and color. As methods of investigation improved, attention turned towards demonstration of foreign substances in the urine, and, even more so, the quantitative changes in its normal components. Traube and Jochmann [1] discovered that the urine of fever patients contains more urea than that of healthy individuals; and Salkowski [2] demonstrated that the excretion of potassium salts increased while that of sodium decreased during fever. Increases in phosphoric acid and sulphuric acid excretion during fever were also established. All these were such constant accompanying phenomena of a febrile condition that they were soon counted among the indisputable criteria of the pathology of fever. The behavior of chlorides during fever only became subject of investigation at a later date, and the scarcity of research papers on chloride excretion as compared to the numerous investigations on the behavior of urea is striking. Redtenbacher [3] was the first investigator who found that in genuine pneumonia chlorides decrease, or even disappear altogether from the urine. Unruh [4] found decreases in chloride during febris recurrens and typhoid fever which, at times, were even more considerable than in pneumonia patients. Rohmann [5] found no chloride retention in ileotyphus. Lehmann [6] stated that the low alkali-chloride content of urine existed only a very short time, never had he observed it to last more than three days. But no one before Rohmann examined the causes of the decrease in chlorides during fever. He was the first in this area -- and has so far been the only one -- who

in 1879 determined the amounts of NaCl taken up and excreted in three pneumonia patients -- thus pioneering the only way in which this problem can be solved. He too found decreases in chloride excretion. Since then nobody has investigated the conditions of chloride metabolism during an acute attack of fever.

A decrease or increase in NaCl excretion as such is of no pathological interest whatever, since it has no physiological limitation. During starvation, for instance, chloride decreases considerably or may even disappear entirely. On the other hand when the salt content of the food is high, amounts of NaCl excretion over a 24 hour period may far exceed 20 g. Voit (1860) has demonstrated that examinations of chloride excretion can only be correct when we compare the exact amount of salt taken up in the food with that excreted in urine and feces. Under normal conditions, when resorption is undisturbed, renal function unimpaired, when there are no congestions or edema, the same conditions govern the excretion of chloride as that of N_2, i.e., the difference between the quantity of NaCl taken up with the food and that excreted in urine and feces indicates how many g of NaCl the organism has gained or lost over a period of 24 hours. It must be noted that, as in the case of N_2-metabolism the balance between uptake and excretion -- the chloride equilibrium -- is only attained gradually over a few days. When there is a sudden increase in supply less NaCl is at first excreted, or in a sudden reduction of supply more, than the quantity contained in the food. On the basis of these laws it is clear that our results will be more accurate the longer the span of time over which our experiments are continued, and the less the fluctuations in the sodium chloride content of the food from day to day.

I have set myself the task to examine chloride metabolism in acute febrile diseases. I have conducted these experiments in the 1st Medical Clinic during a period during which its direction was assigned to me. The experiments were conducted in the following manner: I weighed the quantities of food eaten by the patients every 24 hours, as well as the quantities of urine and feces excreted by them. In order to avoid errors the patients, who were under strict control, received their food in containers graduated in cm^3, which were not refilled until the patient had eaten its entire contents. This control is indispensable and its results quite accurate inasmuch as the patients received only milk, soup and water. Only those whose condition permitted it also received rolls. I have determined the NaCl content of the milk, soup and water daily; if the patient received rolls I also weighed these and determined their NaCl content. I also took care that the patients

remained in bed during fever-free periods. There was no need to watch this particularly during febrile periods. During the two days prior to the start of the investigation the patients received equal amounts of milk and soup as far as possible to prevent the influence of a preceding nutrition richer or poorer in NaCl. I had the urine collected over a suitable period -- from 9 a.m. until 9 a.m. the following morning; I had the patient empty his bladder a few minutes before the end of this period. After the quantity of urine of the 24 hour period had been measured, I determined its NaCl content. The feces were collected over a period of 24 hours, weighed, and their NaCl content determined. In patients suffering from constipation I collected the feces over several days and divided the NaCl content over as many days as the constipation had lasted.

By chloride I understand the most important chloride compound of the organism, sodium chloride. In the tables below the entire amount of chloride taken up and excreted is calculated as sodium chloride.

For quantitative determination of the chloride content of the food, as well as that of urine and feces, I used Vollhard's titration method which yields most reliable results. After evaporation of given quantities of food, in a platinum vessel, with sodium carbonate on a water bath and carborization, the NaCl content of the ash was determined according to Vollhard's method. Prior to determining the NaCl content of the rolls and the feces -- these were dried at 110° and weighed -- this also gave us the water content of the feces -- the substances were then carborized.

My investigations were conducted in pneumonia, typhus and malaria patients. These three diseases are the three typical forms of febrile diseases. The following gives details on these various forms of disease.

I. Pneumonia

Five patients were investigated: three cases of typical pneumonia, one case of catarrhal pneumonia and one case of pneumonia migrans.

For the representation of the course of chloride excretion I have only used the data of one patient (Al. K.) (see Table 1). This patient was under observation from the third day of pneumonia attack on. Special columns in the table indicate the amount of food taken up during 24 hours and its percentage of sodium chloride; the daily quantity, specific weight and NaCl content of the urine; further, the quantity of sodium chloride excreted with the feces; finally, the total quantity

TABLE I. Pneumonia

Excretion of Chlorides During Fever

(1) Datum	(2) Name	(3) Krankheit	(4) Temperatur	(5) Harnmenge in 24 Stdn. ccm	(6) Spez. Gew.	(7) ClNa in 24 Stunden g	(8) Wasser und ClNa im Koth	(9) Milch in 24 Stunden ccm	(10) ClNa der Milch pCt.	(11) Suppe in 24 Stunden ccm	(12) ClNa der Suppe pCt.	(13) Trinkwasser in 24 Std. ccm	(14) ClNa des Trinkwassers pCt.	(15) Summe ClNa aufgenommen in der Nahrung g	(16) Flüssigkeits-Einnahme ccm	(17) Wasseraufnahme durch Arzneimittel	(18) Wasserausscheidung durch Haut u. Lungen
22. III.	AL. K.	(19) Typ. Pneumonie	40,4	1450	1022	6,96	(20) In 5 Tagen 400 g Wasser u. 0,26 g ClNa	1700	0,2	750	0,8	1500	0,01	9,55	3950	(21) Inf. ipecac. In 5 Tagen = 640 g	Täglich 800 g gerechnet in 5 Tagen = 4000 g
24. III.	"	"	40,6	1940	1016	6,21		2250	0,2	400	0,8	800	0,01	7,98	3550		
25. III.	"	"	40,5	2380	1014	4,53		2000	0,22	500	0,89	1000	0,01	8,95	3900		
26. III.	"	"	40,3	2420	1014	2,90		970	0,22	500	0,92	1000	0,01	7,89	2450		(21a)
27. III.	"	"	Krise	1400	1019	0,84		2000	0,12	500	0,8	700	0,01	5,27	2200		

(22) Gesammt-Einnahme von Wasser (Milch, Suppe, Trinkwasser, Arznei) in 5 Tagen = 16280 ccm. Gesammt-Einnahme von ClNa = 39,54 g.
(23) " Ausgabe " " (Harn, Koth, Lunge und Haut) " 5 " = 14140 " " Ausgabe " ClNa = 21,70 g.
(24) Es stellt sich heraus eine Retention im Körper von 2150 ccm Wasser und 17,94 g ClNa, dasselbe entspricht einer 0,82proc. ClNa-Lösung.

(A) **Ausscheidung der Chloride nach der Krise.**

28. III.	"	"	—	1300	1021	1,84	(25) In 14 Tagen 357,8 g Wasser und 0,7 g ClNa	1100	0,12	400	0,8	200	0,01	4,54	1700	(26) Inf. ipecac. In 14 Tagen = 1120 g	(27) Täglich 800 g gerechnet in 14 Tagen = 11200 g
29. III.	"	"	—	1200	1028	3,00		1500	0,13	400	0,8	500	0,01	4,81	2250		
30. III.	"	"	—	1000	1028	5,40		1500	0,12	500	0,8	—	0,01	5,80	2000		
31. III.	"	"	—	1620	1025	8,26		2000	0,2	600	0,8	50	0,01	8,80	2650		
1. IV.	"	"	—	3110	1011	7,15		3500	0,12	800	0,8	—	—	10,60	4350		
2. IV.	"	"	—	3100	1012	9,61		2950	0,12	800	0,8	—	—	9,94	3750		
3. IV.	"	"	—	3360	1010	9,74		3000	0,12	800	0,8	—	—	10,00	3800		
4. IV.	"	"	—	3940	1009	10,21		3500	0,12	800	0,8	—	—	10,60	4300		
5. IV.	"	"	—	3220	1010	10,95		4250	0,12	800	0,8	—	—	11,50	5050		
6. IV.	"	"	—	3450	1010	11,01		3000	0,12	800	0,8	—	—	10,00	3800		
7. IV.	"	"	—	3830	1009	11,49		3500	0,12	800	0,8	—	—	10,60	4300		
8. IV.	"	"	—	4160	1009	12,04		4500	0,12	800	0,8	—	—	11,80	5300		
9. IV.	"	"	—	4120	1009	12,36		4000	0,15	800	0,75	—	—	12,00	4800		
10. IV.	"	"	—	3420	1010	12,31		4000	0,15	800	0,75	—	—	12,00	4800		

(28) Gesammt-Einnahme von Wasser (Milch, Suppe, Trinkwasser, Arznei) in 14 Tagen = 54790 ccm. Gesammt-Einnahme von ClNa = 132,99 g.
(29) " Ausgabe " " (Harn, Koth, Lunge und Haut) " 14 " = 53570 " " Ausgabe " ClNa = 126,13 g.
(30) Es stellt sich heraus eine Retention im Körper von 1283 ccm Wasser und 6,86 g ClNa, dasselbe entspricht einer 0,5proc. ClNa-Lösung.

1 -- Date; 2 -- Name; 3 -- Disease; 4 -- Temperature; 5 -- Quantity of urine in 24 hours; 6 -- Specific weight; 7 -- NaCl in 24 hours; 8 -- Water and NaCl in feces; 9 -- Milk in 24 hours; 10 -- NaCl of the milk; 11 -- Soup in 24 hours; 12 -- NaCl in the soup; 13 -- Drinking water in 24 hours; 14 -- NaCl of drinking water; 15 -- Total of NaCl uptake in food; 16 -- Liquid uptake; 17 -- Water taken up with medicines; 18 -- Water excreted through skin and lungs; 19 -- Typical pneumonia; 20 -- in 5 days 400 g water and 0.26 g NaCl; 21 -- Infusion. In 5 days 640 g; 21a -- 800 g

daily calculated from 5 days at 4140 g; 22 -- Total amount of water (milk, soup, drinking water, medicine) in five days -- 16,290 cc. Total uptake of NaCl -- 39.54 g; 23 -- Total excretion of water (urine, feces, lungs and skin) in 5 days -- 14,140 cc. Total excretion of NaCl -- 21.70 g; 24 -- It follows that the body retained 2150 cc water and 17.94 g NaCl, which corresponds to a 0.82% NaCl solution; A -- Excretion of Chlorides After the Crisis; 25 -- In 14 days 587.8 g water and 0.7 g NaCl; 26 -- Infusions in 14 days -- 1920 g; 27 -- Daily 830 g calculated from 14 days -- 11,620 g; 28 -- Total uptake of water (milk, soup, drinking water, medicines) in 14 days -- 54,720 cc. Total uptake of NaCl -- 132.99 g; 29 -- Total excretion of water (urine, feces, lungs and skin) in 14 days -- 53,370 cc. Total excretion of NaCl -- 126.13 g; 30 -- I.e., the body retained 1383 cc water and 6.86 g NaCl which corresponds with a 0.5% NaCl solution.

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of liquids and sodium chloride taken up and excreted during 24 hours. For greater clarity I have printed the columns to be specially taken into consideration and compared in bold print. The table shows that chloride excretion diminishes gradually during the first fever cycle up to the day of crisis. On that day only 0.84 g NaCl was contained in the urine excreted over 24 hours. When we compare the quantities of NaCl taken up with the food with those excreted in urine and feces, we can see that the patient excreted less than he ingested each day. The difference rises gradually up to the peak of the pneumonia attack. I have continued to examine chloride metabolism in this patient in a second cycle for 14 days starting on the day after crisis. These data can be seen in the second part of the table. They show a slight increase on the day following the crisis. On the second day 3 g NaCl were excreted, on the third day 5.40 g, on the fourth day 8.26 g and later even 11 and 12 g. We see, furthermore, from this table that there is a considerable increase in NaCl excretion between the third and fourth day after the crisis. On the same day daily quantities of urine also began to rise and this rise could be observed for a long time. At the end of the second week -- the end of my investigation -- the daily quantity of urine was 3,420 cm3 with 12.31 g NaCl. The food ingested by this patient consisted throughout of milk, soup and rolls. Those patients who were also given meat and rise from the time at which their condition permitted, even excreted 20-27 g NaCl over 24 hours, as their convalescence progressed. But I could observe in these patients also that there was a considerable increase in NaCl excretion, a few days after their crises, up to daily amounts of 10-11 g. During the period of copious feeding, this was expressed by higher NaCl excretion values as mentioned above.

I would further mention that one patient excreted 12.36 g NaCl on the fifth day after the crisis. On this day fever recurred and a pleuritic exudate could be observed. Two days later excretion already diminished to 4 g and it even decreased to 2 g with increased exudate and temperature. After complete resorption of the exudate and return of temperatures to normal it increased again to 16-17 g. I examined chloride excretion for 37 days in this patient.

At the end of each cycle -- by comparing total uptake and excretion -- I calculated the ratio of liquid and sodium chloride taken up and the loss of water of the organism through urine, feces, lungs and skin, and loss of NaCl excreted through urine and feces. I will return later to the conclusion which I derived.

These metabolism experiments have shown that chloride excreted in relation to uptake, decreases considerably during an attack of pneumonia. I found this regular decrease both in the two cases of atypical pneumonia and in the three croupous pneumonia cases. On the fourth-fifth day after the crisis (see Table I) the values for uptake and excretion were close to each other; on the sixth day some chloride was retained again; and from then on through the 10th day uptake and excretion were about equal. From the 11th day to the end of the experiment -- through five days -- the NaCl excretion increased constantly. Rohmann claims that retention usually stops after the crisis, being replaced by the so-called epicritical increase in excretion. But even in his cases retention could be observed time and again after the crisis. After the epicritical increase at the start of convalescence he often observed a renewed decrease of excretion but he admits -- though he did not continue his own investigations beyond this point -- that excretion values rise again later.

What is the cause for this considerable degree of retention of chlorides in the organism? Investigators were at first of the opinion that it is due to diminished appetite and food uptake. Traube thought that chlorides ingested with food are not resorbed completely from the intestines. A further possibility which was considered was that while resorption might be complete, the substances were not excreted through the kidneys. Rohmann has demonstrated that imperfect resorption of the chlorides cannot be the cause for diminished excretion because the feces contained only little chloride, thus the chlorides must be retained by the organism. My own investigations are in accordance with this finding. Malfunction of the kidneys can also be excluded as a cause for retention -- as Klees opined. In acute hemorrhagic nephritis with its attendant intense impairment of the renal glomerulus, chloride excretion is

decreased much less than is the case in pneumonia patients. Rohmann postulated that the cause of retention must be sought in the ratio of circulating protein to sodium chloride in the blood plasma. He attributes it to increased protein breakdown. Basing himself on Voit's theory, building on Forster's concepts, he considers the transition of organic protein to circulating protein to be the cause of the decrease in chloride excretion. Forster [7] had found that the regulation of chloride metabolism was governed by the protein metabolism. When large amounts of chloride-requiring proteins reach the circulation they bind a corresponding amount of free chlorides circulating in the plasma. If this relation between protein and NaCl, postulated by Rohmann, would indeed obtain, it would have to make itself felt always when the same conditions exist: i.e., whenever a nitrogen-containing tissue in the body disintegrates, a decrease in chloride excretion should be observed. But neither Laudenheimer [8] nor Schopp [9] could confirm this. They both investigated chloride metabolism in carcinoma patients -- protein breakdown is increased in carcinoma patients as well as in fever patients. Also the investigations in fasting subjects are not in accord with Rohmann's postulate. It is further contradicted by the fact that organic protein which changes into circulating protein is also eventually broken down, its nitrogen is excreted as urea, and thus the sodium chloride bound by it ought to be released. But this is not the case.

Redtenbacher held the view that a part of the retained chloride is used to form the exudate and is thus bound to alveolar infiltration. But this view is also incorrect or, at any rate, not entirely satisfactory, for chloride retention is not only a phenomenon encountered in pneumonia; it also occurs in other acute febrile conditions with no significant exudation. My own chloride determinations on croupous lungs also contradict this view. Since no investigations in this direction had been made before, I had to determine the chloride content of normal lungs first for comparison. Only lungs with no <u>in vivo</u> indications of an independent lung ailment were suitable for this purpose, i.e., where there was no factor, such as edema, catarrh or congestion which would make the lung rich in blood and lymph. I am grateful for this material to my assistants, Messrs. Minich, Lovrich and Kenyeres. I conducted the investigations as follows: to remove all blood clots the veins were rinsed with distilled water until the rinsing water remained clear. Then the lung was weighed. I then dissected a piece of lung of definite weight into smaller segments, evaporated them in a porcelain vessel on a water bath, and dried at 110° to constant weight. In each case 1 g of this dried lung was carborized after evaporation in a platinum vessel with soda on a water bath. The ash was dissolved in nitric acid and its sodium chloride content determined according to Vollhard's

method. I examined three normal lungs in this fashion. One was the right lung of a man aged 40 who had died after herniotomy; the weight of the fresh lung was 625 g; its dry weight 151.2 g. In 1 g of dry lung I found -- as an average value of three samples -- 0.C2 g NaCl; thus the entire right lung contained 3.1 g NaCl. The second was the right lung of a 27 year old man who had died suddenly due to rupture of an aneurism. Its fresh weight was 714 g, dry weight 128.5 g. 1 g dry lung -- in an average of three samples -- contained 0.029 g, i.e., the entire right lung had 3.72 g NaCl. The third was the left lung of a 70 year old woman who had died of marasmus senilis. The fresh lung weighed 270 g, the dry weight was 63.3 and in 1 g dry lung -- average value of three samples -- I found 0.017 g NaCl, i.e., 1.1 g for the entire lung. Of the croupous lungs one was the lung of a 56 year old man in a state of hepatization -- only the upper and innermost part of the upper lobe was free and contained air, the rest was infiltrated. The fresh weight of the lung was 1,668 g, dry weight 285.9 g; 1 g dry lung -- on the average -- 0.027 g NaCl or 7.8 g for the entire lung. The second was the right lung of a man aged 33, all three lobes hepatized; fresh weight 2,021 g, after drying 301 g; 1 g on the average contained 0.034 g NaCl -- the entire lung thus 10.28 g. -- Let us assume then the NaCl content of the right lung of a healthy individual as 3.4 g -- and compare this with 10.28 g NaCl found in the right lung with extensive croupous inflammation. We can see that the NaCl content of the croupous lung is about three times that of a normal lung. To put it in figures: the croupous lung contained 6.68 g NaCl more than the healthy one. This represents an important increase in NaCl content but not enough to account alone for the even considerably larger sodium chloride retention observed in the course of croupous pneumonia. As will be seen from the Table 17.94 g NaCl were retained in the course of five days of a pneumonia attack.

I have also examined the chloride content of the sputum of pneumonia patients. NaCl content of 24 hour sputum during the fever fluctuated between 0.3-0.5 g; after the crisis between 0.3-0.4 g. The NaCl content of perspiration I found to be between 0.25-0.3%. This corresponds to the findings by other authors in healthy individuals. Thus, the NaCl content of both sputum and perspiration is so low that it can be disregarded in metabolism investigations. It can in no way account for the decreased chloride excretion observed during fever.

The problem of chloride retention has also been dealt with in our Medical Association in 1887 when Prof. von Koranyi gave a talk on fibrinous pneumonia. In the course of the discussion Prof. Liebermann indicated that no explanation for

chloride retention was available to date. He drew attention to the theory of some investigators according to whom chlorides are said to disappear during croupous pneumonia because NaCl is a histogenetic substance required by the organism for producing tissue. In the middle of the 70's Liebermann conducted experiments in Remboldt's clinic taking as his point of departure the postulate that in NaCl were indeed a histogenetic substance, a chloride which is not a histogenetic substance, such as for instance calcium chloride which on the contrary is a purgative, should be excreted. With this in mind he gave pneumonia patients milk whose exact chloride content was known to him. He then gave them a definite quantity of NaCl and an equal quantity of calcium chloride. Neither the NaCl nor the calcium chloride appeared in the urine. This proves that the above hypothesis is untenable.

None of the experiments carried out to date and hypotheses built on them can, therefore, supply a satisfactory explanation for chloride retention. There remains Leyden's [10] assumption of 1870 according to which chloride retention is due to the fact that the febrile organism retains water, thus the tissues become more waterlogged, and with this increase in water the ability of the tissue to absorb NaCl also increases. Laudenheimer who investigated chloride metabolism in carcinoma patients found that chloride retention which is sometimes observed in such patients, is due to water retained by the organism. He expressed the opinion that the same might be true in fever patients. My own experiments lend some support to this line of thinking. Before I go further into this, I must mention the physiological relation between water and salt excretion. F. Hoppe-Seyler's [11] investigations have shown that the sodium chloride content of the various body fluids (blood, lymph, cerebrospinal fluid) under normal conditions, is pretty stable at about 0.6%. Since NaCl dissolves very readily in water, there can be no physical cause for this behavior, that an equal amount of salt is excreted as has been taken up. According to Ponfick [12] it is possible to inject a dog with large quantities of dog blood serum without increasing the amount of urine in the least, while any other uptake of water at once increases renal function. Kulz [13] made the same observation when he administered various concentrations of sodium chloride to an animal's vascular system. These observations imply that the organism is not sensitive toward an increase in fluids, provided that the sodium chloride percentage of the fluids remains stable. This sodium chloride concentration regulates the entire fluid balance if we consider that increased NaCl supply, whose excretion requires a certain amount of fluids, increases the quantity of urine excreted, irrespective of whether the organism contains sufficient water or not. If it does not --

Voit postulates -- the required amount of water is withdrawn from perspiration. Conversely, if the body's water content is increased for one reason or another, its chloride content must rise proportionally. If the necessary salt is not supplied in the food, chlorides are withheld from renal excretion. We are, therefore, justified in our assumption that a close relationship, which is subject to definite rules, exists between the salt- and water content of the body.

This quantitative relation between NaCl and body fluids is of great biological significance. Buchner's [14] experiments can be explained on this basis. He found that blood serum can inhibit the development of bacteria even outside the body, but, when it is diluted with distilled water it loses this vital property. On the other hand seven times that amount of a 0.7% NaCl solution can be added to the serum without changing its globulicidal and bactericidal activity. All this makes it appear very likely that it is the changed water content of the organism which influences chloride excretion in acute attacks of fever also, and that the NaCl ratio of all body fluids remains constant also here, independently of all other metabolic influences. Further indications in this direction are given by the investigations of Runeberg [15], who found an average of 0.65% sodium chloride in the exudates of 15 carcinoma patients; also by those of Laudenheimer who found 0.61% NaCl in ascites in a case of peritoneal carcinoma; and 0.7% in a case of stomach cancer. In the tables I have given exact calculations of the proportion of salt and water retained a the end of each cycle. During the first five day fever cycle, taking into consideration the entire uptake and excretion of fluids and salt, we can see that over the five day period 17.94 g NaCl and 2,150 cc water were retained, i.e., 0.82 g NaCl per 100 cc water, which means that the ratio between salt and water corresponds to an 0.82% sodium chloride solution. During the second -- fever-free cycle -- 6.88 g NaCl and 1,383 cc water were retained, which corresponds to an 0.5% sodium chloride solution. These values are close to the physiological sodium chloride solution. They thus support the hypothesis that the organism strives to maintain the physiological adjustment of its fluids even under pathological conditions, such as febrile diseases. It follows from this that during an attack of pneumonia the body retains amounts of water and NaCl in proportions which correspond to the physiological sodium chloride solution.

II. Abdominal Typhus

In three out of four patients I merely determined the chloride content of the urine excreted throughout the day, and

did not determine chloride content of the food or the feces. In the first patient chloride content was determined for seven days only. The smallest amount of NaCl excreted during the fever was 1.04 g - this rose to 10 and 10.48 g during the first fever-fever free days. The second patient's chloride excretions were examined through 11 days of fever and 25 fever-free days. The smallest amount of NaCl excreted was 0.7 g in 1,500 cc urine over one day. From then on daily quantities of urine as well as its chloride content increased gradually. On the sixth fever-free day the daily amount of urine excreted was 2,800 cc with 17.64 g NaCl -- this value was increased to constant high values of around 20 g when a diet of meat was reintroduced. Polyuria as well as increased NaCl excretion persisted for a long time -- on the 25th fever-free day the daily amount of urine excreted was still 3000 cc with a NaCl content of 25.8 g. In the third case I examined the urine through 13 fever and 22 fever-free days and found a very similar course of chloride excretion.

In the fourth case I have conducted metabolism examinations over four periods of time. Table II shows the behavior of chloride excretion during each period. One can note a significant retention during four days of continuous fever; this is much reduced during the first three fever-free days. On the fourth fever-free day 7.9 g were excreted with the urine and 0.22 (0.9:4) with the feces, or a total of 8.12 g. Uptake was 8.10 g, which means that excretion was insignificantly increased compared to uptake. But retention was observed again on the 7th, 8th and 13th fever-free day. I calculated the ratio between the water and the chloride retained at the end of each cycle. I found this to correspond to a 0.55% sodium chloride solution at the end of the first cycle, 0.7% solution at the end of the second cycle and 0.4% at the end of the third and fourth cycles. Thus there is chloride retention during fever also in typhus patients, and an increased excretion starting approximately on the 4th to 7th fever-free day. But investigation of the metabolism demonstrated that there is no significantly increased sodium chloride excretion as compared to uptake here. Apart from the fourth fever-free day mentioned above, I found that there was still a measure of water and chloride retention on the 7th, 8th and even 13th fever-free day. In my opinion the only interpretation for this that the organism does not release the sodium chloride retained during the fever period at once during the first fever-free days, but retains this for the reconstruction of the tissues decayed during the long fever period, just as we know to be the case with N_2. Only later, with copious nutrition do high sodium chloride excretion values appear. And it is possible that then there is an increased excretion as compared to uptake. Thus I did not

Table II. Abdominal Typhus

I. Cycle. Febris Continua

(1) Name	(2) Krankheit	(3) Datum	(4) Temperatur	(5) Harnmenge in 24 Stdn. ccm	(6) Spec. Gewicht	(7) ClNa in 24 Stunden g	(8) Wasser u. ClNa im Koth	(9) Milch in 24 Stunden ccm	(10) Suppe in 24 Stunden ccm	(11) ClNa d. Milch pCt.	(12) ClNa d. Suppe pCt.	(13) Trinkwasser in 24 Stunden	(14) ClNa d. Trinkwassers pCt.	(15) Summe des ClNa, aufgenommen in d. Nahrung g	(16) Flüssigkeits-Einnahme ccm	Wasseraufnahme durch Aerzneimittel	(17) Wasserausscheidung durch Haut u. Lunge
M. H.	(18) Typh. abd. in der dritten Woche	4. II.	38,4—39,6	1600	1021	9,08	150 g Wasser und 0,48 g ClNa.	3000	200	0,15	1,08	—	—	6,66	3200	—	
"		5. II.	38,4—39,0	1650	1019	3,12		2255	200	0,15	1,08	—	—	5,34	2455	—	
"		6. II.	38,4—39,5	1260	1021	3,00		2255	400	0,15	1,08	—	—	7,74	2655	—	
"		7. II.	38,4—39,5	1420	1022	4,26		3000	200	0,15	1,08	—	—	6,66	3200	—	

(22) Gesammt-Einnahme von Wasser (Milch, Suppe) in 4 Tagen = 11510 ccm. (24) Gesammt-Einnahme von ClNa = 26,56 g.
(23) " Ausgabe " " (Harn, Koth, Lunge u. Haut) in 4 Tagen = 9329 ccm. (25) " Ausgabe " " = 14,59 g.
(26) Es stellt sich heraus eine Retention im Körper von 2181 ccm Wasser und 11,97 g ClNa, dasselbe entspricht einer 0,55 proc. ClNa-Lösung.

(A)

II. Cyclus. Die 4 ersten fieberfreien Tage.

"	"	23. II.	—	1910	—	4,50	150 g Wasser und 0,45 g ClNa.	2750	200	0,14	0,93	—	—	5,72	2950	—	
"	"	24. II.	—	1700	—	4,59		2500	400	0,14	0,9	—	—	7,15	2900	—	
"	"	25. II.	—	2650	1008	6,99		3500	400	0,14	0,9	—	—	8,50	3900	—	
"	"	26. II.	—	3650	1006	7,90		4500	200	0,14	0,9	—	—	8,10	4700	—	

(29) Gesammt-Einnahme von Wasser (Milch, Suppe) in 4 Tagen = 14550 ccm. Gesammt-Einnahme von ClNa = 29,47 g.
(30) " Ausgabe " " (Harn, Koth, Lunge u. Haut) in 4 Tagen = 13899 ccm. " Ausgabe " " = 24,88 g.
(31) Es stellt sich heraus eine Retention im Körper von 651 ccm Wasser und 4,59 g ClNa, dasselbe entspricht einer 0,7 proc. ClNa-Lösung.

(B)

III. Cyclus. Der 7. und 8. fieberfreie Tag.

M. H.	Typh. abd. in der dritten Woche	2. III.	—	4500	1008	9,45	3519 g Wasser und 0,57 g ClNa	6500	400	0,17	0,98	—	—	14,97	6900	—	
"		3. III.	—	5320	1008	9,57		7000	200	0,16	0,96	—	—	13,12	7200	—	

(34) Gesammt-Einnahme von Wasser (Milch, Suppe) in 2 Tagen = 14100 ccm. Gesammt-Einnahme von ClNa = 28,09 g.
(35) " Ausgabe " " (Harn, Koth, Lunge u. Haut) in 2 Tagen = 11815 ccm. " Ausgabe " " = 19,09 g.
(36) Es stellt sich heraus eine Retention im Körper von 2285 ccm Wasser und 9 g ClNa, dasselbe entspricht einer 0,4 proc. ClNa-Lösung.

[Continued on following page]

Cycle IV. The 13th Fever-Free Day

(1) Name	(2) Krankheit	(3) Datum	(4) Temperatur	(5) Harnmenge in 24 Stunden ccm	(6) Spec. Gewicht	(7) ClNa in 24 Stunden g	(8) Wasser u. ClNa im Koth	(9) Milch in 24 Stunden ccm	(10) Suppe in 24 Stunden ccm	(11) ClNa d. Milch pCt.	(12) ClNa d. Suppe pCt.	(13) Trinkwasser 24 Stunden	(14) ClNa d. Trinkwassers pCt.	(15) Summe d. ClNa, aufgenommen in der Nahrung g	(16) Flüssigkeits-Einnahme ccm	(17) Wasseraufnahme durch Arzneimittel	(18) Wasserausscheidung durch Haut und Lungen	(19)
.	.	8. III.	—	4850	1007	12,28	(37) 200 ccm Wasser und 0,31 g ClNa	5000	800	0,14	0,9	3 Eier	0,103	15,72	6800	—	830 g	

(38) Gesammt-Einnahme von Wasser (Milch, Suppe) in 1 Tag = 6800 ccm. Gesammt-Einnahme von ClNa = 15,72 g
(39) . Ausgabe . . (Harn, Koth, Lunge und Haut) in 1 Tag = 5900 ccm. . Ausgabe . . = 12,41 g.
(40) Es stellt sich heraus eine Retention im Körper von 200 ccm Wasser und 3,31 gClNa, dasselbe entspricht einer 0,4 proc. ClNa-Lösung.

1 -- Name; 2 -- Disease; 3 -- Date; 4 -- Temperature; 5 -- Quantity of urine in 24 hours; 6 -- Specific weight; 7 -- NaCl in 24 hours; 8 -- Water and NaCl in feces; 9 -- Milk in 24 hours; 10 -- Soup in 24 hours; 11 -- NaCl of milk; 12 -- NaCl of soup; 13 -- Drinking water in 24 hours; 15 -- Total NaCl taken up with food; 16 -- Liquid uptake; 17 -- Water taken up with medicine; 18 -- Water excreted through skin and lungs; 19 -- Abdominal typhus in the third week; 20 -- 159 g water and 0.23 g NaCl; 21 -- 830 g daily calculated from four days at 3320 g; 22 -- Total uptake of water (milk, soup) in four days -- 11,510 cc; 23 -- Total excretion of water (urine, feces, lungs, skin) in four days -- 9329 cc; 24 -- Total uptake of NaCl -- 26.56 g; 25 -- Total excretion of NaCl -- 14.59 g; 26 -- i.e., the body retained 2181 cc water and 11.97 g NaCl which corresponds to a 0.55% NaCl solution; A -- Cycle II. The First Four Fever-Free Days; 27 -- 669.9 g water and 0.9 g NaCl; 28 -- 830 g daily calculated from four days at 3320 g; 29 -- Total uptake of water (milk, soup) in four days -- 14,550 cc. Total uptake of NaCl -- 29.47 g; 30 -- Total excretion of water (urine, feces, lungs and skin) in four days -- 13,899 cc. Total excretion of NaCl -- 24.88 g; 31 -- i.e., the body retained 651 cc water and 4.59 g NaCl, which corresponds to a 0.7% NaCl solution; B -- Cycle III. The Seventh and Eighth Fever-Free Days; 32 -- 355.9 g water and 0.87 g NaCl; 33 -- 830 g daily calculated in two days of 1660 g; 34 -- Total uptake of water (milk, soup) in two days -- 14,100 cc. Total uptake of NaCl -- 28.09 g; 35 -- Total excretion of water (urine, feces, lungs, skin) in two days -- 11,815 cc. Total ex-

cretion of NaCl -- 19.09 g; 36 -- i.e., the body retained 2285 cc water and 9 g NaCl corresponding to an 0.4% NaCl solution; 37 -- 220 g water and 0.13 g NaCl; 38 -- Total uptake of water (milk, soup) in one day -- 6800 cc. Total uptake of NaCl -- 15.72 g; 39 -- Total excretion of water (urine, feces, lungs, skin) in one day -- 5900 cc. Total excretion of NaCl -- 12.41 g; 40 -- i.e., the body retained 900 cc water and 3.31 g NaCl corresponding to an 0.4% NaCl solution.

observe the so-called "epicritical" NaCl excretion dwelt on by other authors. In my observations there was only one such day where more NaCl was excreted than ingested. This much is certain: as the fever-free days progress ever larger amounts of NaCl are excreted within a 24 hour period, without, however, exceeding the quantities of NaCl ingested. My investigations further demonstrate that chloride retention is not of as short a duration as is postulated by Lehmann, but can be observed throughout the entire febrile period. Increased NaCl excretion and polyuria which set in during convalescence may last up to 2-3 weeks. The ratio between the water and chloride retained is close to that of physiological sodium chloride solution. It is thus apparent that -- as in the case of pneumonia attacks -- here too the organism strives to maintain the concentration of sodium chloride in its fluids during the fever.

III. Malaria

I have investigated chloride metabolism in three patients. In two cases the diagnosis was assured since the fever set in at the typical time, excluding the possibility of another disease with intermittent periods of fever. In the third case intermittent, irregular periods of fever occurred. But there was no doubting the diagnosis in this case either. In all three patients large, round plasmodia with numerous pigment granules were found free in the blood. The latter had in part a dot-like, and, in part, a rod-shaped appearance. Two zones could be distinguished clearly in the plasmodia: an external, darker zone, which alone contained the pigment granules, and an inner lighter zone. Furthermore, in addition to blood corpuscles very active fibrillation, and, within the blood corpuscles, sporulation, could be observed.

Table III illustrates NaCl metabolism in the first patient, a case of quartan malaria.

Comparing the quantity of urine collected during the period between the onset of the fever and its decline with that collected during the period before and after the fever period, to the end of the daily cycle, we can see that the quantity of

urine excreted during the fever attack was constantly larger than that collected before and after the fever. We have further demonstrated that larger amounts of NaCl were excreted with the portion of urine stemming from the fever period than with those collected before and after it. On 9 Jan, for instance, the following proportions were observed:

First portion	(prior to fever)	120 cc, NaCl therein = 1.716 g
Second portion	(during fever attack)	820 cc, NaCl therein = 6.232 g
Third portion	(after fever attack)	420 cc, NaCl therein = 1.428 g

And on 11 Jan, another day of fever attack:

First portion	(prior to fever)	330 cc, NaCl therein = 3.20 g
Second portion	(during fever attack)	1120 cc, NaCl therein = 9.07 g
Third portion	(after fever attack)	380 cc, NaCl therein = 0.87 g.

During the two fever-free days following the fever attack constant sodium chloride retention was found.

During the first fever-free days the daily amount of urine excreted was usually slightly less than normal, while the total of the three portions of urine collected on the day of a fever attack exceeded normal daily quantities.

From 15 Jan-24 Jan the patient was given daily doses (10-40 cg) of methylene blue. During this period he had two attacks of fever. Fever subsided entirely after 20 Jan [sic]. Examination of chloride metabolism during the period after fever yielded the results below:

	(1)	(2)	(3)	(6)		(4)
28.1.:	Zufuhr 15,40,	ausgeschieden	17,81 g	ClNa,	Bilanz = 2,35 g	Mehrausscheidung
29.1.:	„ 15,25,	„	15,72	„	„ = 0,54	„
30.1.:	„ 16,35,	„	16,28	„	„ = 0,07	Retention (5)

1 -- Uptake; 2 -- Excreted; 3 -- NaCl; 4 -- Excess excretion; 5 -- Retention; 6 -- Balance.

On 30 Jan retention was so slight that one would be justified in stating that already on the third day equilibrium was re-established in the chloride metabolism. The fact that fever attacks did not recur in the patient -- whom we continued to keep under observation -- would also be in agreement with this finding.

Table III. Malaria

Fever-Free Day

(1) Datum.	(2) Name.	(3) Fieber-typus.	(4) Harn-menge in 24 Stdn. ccm	(5) ClNa in 24 Stdn. g	(6) ClNa im Koth. g	(7) Milch in 24 Stdn. ccm	(8) ClNa der Milch. pCt.	(9) Suppe in 24 Stdn. ccm	(10) ClNa der Suppe. pCt.	(11) Trink-wasser in 24 Stdn. ccm	(12) ClNa des Trink-wassers. pCt.	(13) Semmel in 24 Stdn.	(14) ClNa der Sem-mel. pCt.	(15) Gesammt-Einnahme von ClNa in 24 Stdn. g	(16) Gesammt-Ausgabe von ClNa in 24 Stdn. g
5. I.	Al. Sz.	Febr. quartana (17)	1300	10,40	0,17	1500	0,24	600	1,1	—	0,01	1	0,85	11,05	10,57
		0,48 g ClNa wurde retinirt (18)													
		(A) Fiebertag. Max. Temp. 40,6° C.													
6. I.	"	"	1500	12,37	kein Stuhl (19)	1800	0,25	800	1,2	1000	0,01	3	0,86	10,69	12,37
		1,68 g ClNa mehr ausgeschieden (20)													
		(B) Die nächstfolgenden zwei fieberlosen Tage.													
7. I.	"	"	1730	9,26	kein Stuhl (21)	1200	0,19	600	1,005	500	0,01	3	0,85	11,14	9,26
8. I.	"	"	1240	9,92	"	"	"	"	1,006	—	—	3	0,841	10,536	9,92
		7. I. 1,88 / 8. I. 0,67 g ClNa wurde retinirt (22)													
		(C) Der nächstfolgende Fiebertag. Max. Temp. 40,5° C.													
9. I.	"	"	1360	9,37	kein Stuhl (23)	1200	0,208	300	1,08	1200	0,01	1	0,85	6,70	9,37
		(24) 2,67 g ClNa mehr ausgeschieden. (25) Zahl der rothen Blutkörperchen vor dem Fieber 4,120000.													
		(D) Die nächstfolgenden zwei fieberlosen Tage.													
10. I.	Al. Sz.	Febr. quartana (17)	1300	6,50	0,11	1200	0,19	600	1,1	400	0,01	2	0,85	10,45	6,61
11. I.	"		630	5,48	kein Stuhl	900	"	"	1,006	—	—	3	"	9,90	5,48
		10. I. 3,84 / 11. I. 4,42 g ClNa wurde retinirt. (18)													
		(26) Zahl der rothen Blutkörperchen nach dem Fieber 3,170000.													

Continued on following page

The Following Fever Day. Max. Temp. 40.9°C

(1) Datum.	(2) Name.	(3) Fieber-typus.	(4) Harn-menge in 24 Stdn. ccm	(5) ClNa in 24 Stdn. g	(6) ClNa im Koth. g	(7) Milch in 24 Stdn. ccm	(8) ClNa d. Milch. pCt.	(9) Suppe in 24 Stdn. ccm	(10) ClNa der Suppe. pCt.	(11) Trink-wasser in 24 Stdn. ccm	(12) ClNa des Trink-wassers. pCt.	(13) Semmel in 24 Stdn.	(14) ClNa der Sem-mel. pCt.	(15) Gesammt-Einnahme von ClNa in 24 Stdn. g	(16) Gesammt-Ausgabe von ClNa in 24 Stdn. g
12. I.	"	"	1830	13,14	(27) keine Stuhl	1500	0,204	300	0,9	500	0,01	2	"	7,47	13,14
13. I.	"	"	1960	4,80	0,195	1500	0,20	600	0,92	—	—	3	"	10,85	6,995
14. I.	"	"	1680	6,55	(30) keine Stuhl	1800	"	"	0,94	—	—	3	"	11,57	6,55

(25) 5,47 g ClNa mehr ausgeschieden.
(29) Die während des Fiebers gesammelte Harnportion beträgt 1120 ccm, dieselbe enthält:
K_2O . . 7,11 g. Na_2O . . 4,52 g.

E Die nächstfolgenden zwei fieberlosen Tage.

13. I. 5,94 }
14. I. 5,02 } g ClNa wurde retinirt (31)

17

1 -- Date; 2 -- Name; 3 -- Type of typhus fever; 4 -- Quantity of urine in 24 hours; 5 -- NaCl in 24 hours; 6 -- NaCl in feces; 7 -- Milk in 24 hours; 8 -- NaCl of milk, %; 9 -- Soup in 24 hours; 10 -- NaCl of soup; 11 -- Drinking water in 24 hours; 12 -- NaCl of drinking water in %; 13 -- Rolls in 24 hours; 14 -- NaCl in rolls; 15 -- Total NaCl uptake in 24 hours; 16 -- Total NaCl excretion in 24 hours; 17 -- Quartan fever; 18 -- Were retained; A -- Fever Day. Maximum Temperature 40.6°C; 19 -- No feces; 20 -- Excess excretion; B -- Following Two Fever-Free Days; 21 -- No feces; 22 -- Were retained; C -- The Following Fever Day. Max. Temp. 40.5°C; 23 -- No feces; 24 -- Excess excretion; 25 -- Number of red blood cells prior to fever 4,120,000; D -- The Following Two Fever-Free Days; 26 -- Number of red blood cells after fever: 3,170,000; 27 -- No feces; 28 -- Excess excretion; 29 -- The portion of urine collected during the fever was 1120 cc, this contained:; G -- the Next Two Fever-Free Days; 30 -- No feces; 31 -- Were retained.

In one case of quotidian fever I conducted investigations on four successive days. I omit the details which are similar as in the table for the previous case, and will only emphasize the differences observed during the various periods of the fever attack.

On 9 June I collected the urine of this patient every two hours from 9 a.m. on. The results were as follows:

	(1) Temperatur:	(2) Harnmenge:	(3) darin: ClNa	darin: P_2O_5
(4) Vormittag 9—11	37,2—40,6	50 ccm	= 0,47 g	= 0,125 g
„ 11—1	40,6—38,6	240 „	= 2,79 „	= 0,24 „
(5) Nachmittag 1—3	38,6—37,0	70 „	= 0,49 „	= 0,06 „
„ 3—5	37,0—36,6	680 „	= 1,02 „	= 0,27 „
„ 5—7	36,6—36,2	440 „	= 1,44 „	= 0,49 „
(6) Von Abends 7 Uhr bis nächsten Morgen 9 Uhr fieberfrei		1040 „	= 4,06 „	= 2,11 „

1 -- Temperature; 2 -- Quantity of Urine; 3 -- Therein; 4 -- Morning; 5 -- Afternoon; 6 -- From 7 p.m. till 9 a.m. next morning fever-free.

During these two hour periods I also examined the P_2O_5 excretion. The chloride excretion followed the same lines as in the previous patient but due to the daily fever attacks with but brief intervals, excess excretion of NaCl during each isolated attack was not as high as in the previous case of quartan malaria (1st day: 5.16; 2nd day: 1.63; 3rd day: 0.67 g). On the basis of these two-hourly examinations the following facts were established: 1. amount of NaCl excreted rises stepwise with increase in temperature; at the peak of fever more NaCl is excreted than during the first period after the decline in temperature, even though the quantity of urine excreted during the former was only 240 cc while it was 680 cc during the latter; 2. the P_2O_5 excretion behaved in opposite fashion -- at the peak of the fever the lowest values are observed, which increase gradually after the decline of the fever attack.

On 8 June I also determined the quantities of potassium excreted with the 1320 cc of urine. 7.66 g K20 were found in this portion and only much less, 5.21 g Na_2O. According to Salkowski [16] a normal adult excretes 2-3 g K_2O and 4-6 g Na_2O over a 24 hour period. There is thus a considerable increase in potassium excretion.

The third patient was a 32 year old woman with irregular, intermittent attacks of malaria which had lasted for two years. Conditions found in this patient were also analogous. I will refer back to this patient later.

A. Frankel [17] has drawn attention to the paradoxical behavior of chloride excretion in malaria patients -- as compared to other febrile conditions. But opinions on this question are still divided. Prof. v. Koranyi in his clinical lectures, always takes this factor -- which in doubtful cases might be of a diagnostic value -- into consideration. Hertz [18] claims that NaCl as well as urea increase during paraoxysm, while Hovitz and Hammond maintain that there is no change in the NaCl values, and Uhle and Giessler even speak of a decrease in chloride excretion. These conflicting views could not be clarified so far, especially since nobody has up to now investigated chloride metabolism during this disease. My investigations have demonstrated that during an attack of malaria sodium chloride excretion is indeed increased. Kast [19] conducted experiments with toluylene diamine in dogs. This substance dissolves red blood cells without attacking any other tissue. In the course of his experiments Kast found increased chloride excretion, and he suggested that the apparently paradoxical increase in chloride metabolism during malaria might also be connected with the extensive decomposition of red blood cells. I had thought of this possibility even before I learned of Kast's hypothesis, and I conducted my experiments along those lines. It has long been known that red blood cells contain alkali chlorides. Recently Bunge [20] has demonstrated that comparatively ample amounts of NaCl are contained in the dog's red blood cells. It is thus possible that the largest part of the NaCl contained in urine during a fever attack stems from decomposing red blood cells. So far this possibility has only been mentioned, with no tangible results to show. I believe that I will succeed in demonstrating, on the basis of my own investigations, that the source of increased chloride excretion in malaria can, indeed, be none other than the enhanced decomposition of red blood cells.

We know that the malaria toxins, the malaria plasmodia, impair the integrity of red blood cells; they cause them to decompose. Red blood cell counts both prior to and after fever attacks, which have been undertaken with great care by my colleague Franz Tauszk, also prove this point. But this alone is not sufficient proof that the increased chloride excreted can be attributed to this decay of red blood cells. I had to search for other points of support and I found one in the behavior of potassium excretion. I have observed this in two out of three patients, and I found that the urine portion stemming from the febrile stage contained considerably more K_2O than Na_2O. Increased potassium excretion during fever has earlier been attributed to fever erythrolysis. But today we know that its appearance in larger quantities during fever only indicates increased decomposition of the cytoplasm in general,

without necessarily being a specific product of the disintegration of red blood cells. My attention was next focused on urobilin. This urinary pigment was first examined and named by Jaffe, who extracted a substance with similar properties from the bile. Maly obtained a pigment -- which he called hydrobilirubin from bilirubin or biliverdin under the effect of sodium amalgam. We know that hydrobilirubin is identical with Jaffe's urobilin. Whether the latter is always present in normal urine or not is a question on which opinion is divided. Some claim that it is increased during fever, while others state that fever does not influence urobilin at all. It belongs to the group of urinary pigments which originate in the blood; it is a close relative of biliary pigments -- and this is also the reason for its classification by Maly. According to Grimm's [21] investigations the urobilin content of the urine in healthy hungry individuals is low or it may be entirely absent; the same obtains during the period of digestion; but towards the end of the latter or on its completion, significant urobilin excretion may occur and may last up to two hours. It occurred early after raw eggs had been consumed or other foods known to be readily digestible. Grimm explained this behavior by the influence which various nutrient substances exert on biliary secretion. It is known that animal proteins stimulate biliary secretion most strongly; a somewhat lesser effect is exerted by vegetable proteins, and the least effect by fats. On the basis of this he locates urobilin formation in the liver. In his view it is most probable that the cause for urobilinuria bile congestion which occurs under normal conditions, is polycholia. In favor of this view speaks the periodicity of urobilinuria dependent on nutrition and digestion and the simultaneous appearance of biliary pigments in the urine. This hepatogenous theory also has its adherents in France. But in addition to this there are also several other hypotheses on the formation of urobilin which it would be out of order to enumerate here in full. I would only mention that some authors -- for instance, D. Gerhardt [22] -- locate the formation of urobilin in the intestines -- enterogenous hypothesis -- where urobilin, which resulted from the reduction of bilirubin, is resorbed. This view is also shared by Fr. Muller and Maly. But Tissier and other authors assume that hydrobilirubin is a product of hepatic cell malfunction -- insuffisance hépatique. In the light of investigations made to date it seems beyond doubt that urobilirubin is connected with the biliary pigment and thus with the blood pigment and that a primary cause in its formation is the decomposition of red blood cells. Where the transformation takes place, whether in the intestines or in the liver, is a matter of opinion.

Hydrobilirubinuria did not prove of much diagnostic value, the more so since the existence of a urobilinicterus has been

doubted. Only Bergmann used it in 1881 for the determination of concealed and doubtful cases of hemorrhage. G. Hoppe-Seyler [23] did not find significant changes in urobilin excretion in cases of blood anomalies (chlorosis, pernicious anaemia, leukemia). These diseases sometimes do not seem to impair bile formation, and thus do not increase urobilin excretion. According to his investigations urobilin in the urine is increased: 1) in hepatogenous bile congestion where diuresis is ample or bile still reaches the intestines, such as in polycholia; 2) when the colon is congested but not the small intestine; 3) in hemorrhages in internal organs -- during bleeding biliary pigment is formed in ampler quantities from the disintegrating blood pigment. Urobilin in the urine is decreased in: 1) reduction in hepatic function; 2) bile congestion where there is no overflow into the intestine and diuresis is scant; 3) for a certain time after the termination of icterus.

In a later investigation [24] he demonstrated that large doses of tuberculin-injection destroy hemoglobin and polycholia may result, manifesting itself in icterus and ample urobilin excretion. Grimm found increased urobilin excretion in the urine in hematoma and pyemia. With regard to malaria he only says that he always found urobilin in the urine. He does not mention whether it was quantitatively increased or not. In pneumonia patients urobilinuria may at first be absent, but it becomes more ample later, reaching its peak after the crisis. In typhus it is usually absent and in febris continua was only observed when a hepatic complication was also present. Hayem and Schuler made the same findings. The French (Hayem, Tissier, Dujardin-Beaumetz) consider urobilin analysis very valuable. They attribute to it the same significance in recognizing the early stages of hepatic diseases, as is occupied by albumin excretion in recognizing renal malfunction. Much remains to be clarified in this area. We can only state that urobilin is increased during resorption of blood extravasaties and in pathological decay of red blood cells, i.e., where dissociated hemoglobin circulates in the vessels, or in case of bile congestion.

It is difficult to extract urobilin in pure form. Of the quantitative methods of determination the spectroscopic method used by Vierordt and D. Gerhardt is unreliable. Grimm extracted hydrobilirubin from acidified urine with ether or chloroform; evaporated it and dissolved the residue in a few drops of dilute zinc chloride in ammonia water. A grass-green fluorescence resulted. He then diluted the fluorescent solution with measured amounts of water until the fluorescence disappeared. The more dilution was required the larger the quantity of urobilin originally contained in the urine. Hoppe-

Seyler's [25] method for the determination of the urobilin content in urine and feces was a step forward beyond this rather vague method. He obtained satisfactory results with his gravimetric method. He conducted experiments on healthy subjects, including himself. The urobilin values obtained varied slightly, as was to be expected, since the amount of bile, urobilin formation and excretion are interrelated with food uptake. In healthy subjects daily quantities of urobilin excreted in the urine fluctuated between 0.08-0.14 g, an average of 0.123 g. In his opinion this value is not very low, and would have been lower in less well fed individuals, since the subjects investigated were amply nourished. In diseases, such as at the start and termination of icterus, cirrhosis of the liver, and hemorrhages he found 0.216, 0.317 and once 0.420 g urobilin in the urine. Daily quantities of urobilin in the feces of healthy subjects fluctuate -- according to G. Hoppe-Seyler -- between 0.7-3.2 g, an average of 1.7 g.

I have determined quantities of urobilin excreted in urine and feces by malaria patients according to Hoppe-Seyler's method. Urine was examined as follows: to 200 cc fresh urine, acidified with a few drops of dilute sulphuric acid, I added ample amounts of a cold saturated solution of ammonium sulfate. I then left this stand for 24 hours. Thereafter I washed the red flakes of urobilin precipitate on the filter with a concentrated ammonium sulfate solution; extracted the filter, which had been squeezed between pieces of filter paper, repeatedly with equal parts of chloroform and 96 percent alcohol; then I treated the yellow or yellowish-red chloroform — alcohol mixture in a separating funnel with water until the chloroform was well separated. I then evaporated it in a beaker on a water bath, dried at 100°C, filtered the residue, extracted with ether, and -- with the aid of alcohol -- returned the urobilin which remained on the filter to the beaker; evaporated, dried and weighed it. In one patient on the 14th day of icterus catarrh I found 0.128 g urobilin in 100 cc urine -- the amount excreted was thus near the upper limits of the norm; we know that usually urobilin in the urine is increased at the onset and termination of icterus. In three cases of malaria I could only determine urobilin in the urine; the patients were in the Department of Dr. Gyurman. I found 0.16 g in a 24 hour urine portion of one patient, 0.162 g in the second and 0.32 g in the third. The first two patients showed a moderate increase in urobilin excretion, while that of the third was considerably increased -- and this even more so as these patients received only milk and soup. Of the three clinic patients I was able to do a full systematic analysis of urobilin content in urine and feces only in the last one -- due to the time-consuming procedures involved. As mentioned before this patient had a tumor of the spleen, and in addition to irregular, intermittant

fever a slight case of icterus. Only a low bilirubin reaction should be obtained with chloroform from the urine. I have extracted feces collected over 24 hours, after exact weighing, with dilute sulphuric acid and alcohol, stirring frequently during 30 hours. I then determined urobilin content in exactly weighed portions of the extract and have taken the average value of three samples.

I examined the feces twice, in each case on the day after the fever. On 31 August, I found 4.49 g urobilin in the feces, 0.14 g in the urine; on 3 Sept, 0.17 g in the urine, on 4 Sept, 0.212 g, on 5 Sept, 3.03 g in the feces and 0.24 g in the urine. I must emphasize that the patient ate little and, especially on the last day of fever (15 Sept), hardly anything -- which leads one to assume even more that the quantity of urobilin the feces and urine of that day would be increased. But the urobilin content of the feces of 31 August even showed a very considerable rise in comparison with G. Hoppe-Seyler's values found in healthy subjects.

I believe that I have -- on the basis of my investigations -- demonstrated satisfactorily that increased sodium chloride excretion observed during attacks of malaria fever is connected with the decay of red blood cells. Malaria toxins corrode red blood cells. A count showed that their number was considerably diminished after the fever attack. As we have seen, during the fever potassium excretion increased. But this only indicates cytoplasmic decay in general and does not permit any conclusions as to which tissue had disintegrated. In addition to this potential factor a further valuable indication lies in the fact that urobilin excretion during the fever was increased slightly in the urine, but quite considerably in the feces -- compared to values found in healthy subjects, and that even when food uptake was very scant. This finding suggests increased erythrolysis. It is difficult to estimate adequately the quantity of iron from the hemoglobin derivatives, iron and biliary pigments -- on the other hand, hydrobilirubin is the only adequate measure of hemoglobin disintegration. We must assume that after the red blood cells have disintegrated, hemoglobin is retained in the liver and transformed into biliary pigment, polycholia occurs, which occasionally leads subsequently to icterus, and always to an increase in urobilin.

The increased NaCl excretion during the malaria fever attack is replaced by sodium chloride retention during the interval between fever attacks -- during this interval patients excrete less NaCl than they ingest. This is simply due to the fact that the organism retains -- among other components of foodstuffs (noteably N_2) -- also a certain amount of NaCl to

reconstitute the decomposed red blood cells. Only this makes it comprehensible that despite increased appetite during the fever-free interval and increased uptake of food, less sodium chloride appears in the urine and feces than has been ingested. When replacement has been achieved, chloride balance is re-established again during the same period as in the healthy individual.

My investigations can be summarized as follows:

1. NaCl metabolism in acute febrile diseases is considerably different from that which obtains under normal conditions.

2. In pneumonia -- both typical and atypical -- the organism retains NaCl in gradually increasing amounts up to the peak of the attack. Retention can still be observed during the crisis, albeit to a lesser extent, and thereafter excretion begins to increase gradually. In between there may be a brief recurrence of retention (in my case lasting one day). Chloride equilibrium is achieved between the 6th and 10th day, and from the 11th day on more NaCl is excreted than is taken up. Thus the epicritical increase does not occur immediately after the crisis, but only days later, and it may last over a longer period together with ample diuresis which sets in early (on the second to third day after the crisis).

3. The croupous lung contains more NaCl than a healthy lung. The ratio is approximately 1:3. But the amount of NaCl bound by it does not account fully for the quantity of NaCl retained by the organism in the course of pneumonia. NaCl content of sputa and perspiration of pneumonia patients is so insignificant that it can be ruled out as a cause for chloride retention.

4. Experiments made and hypotheses propounded to date cannot adequately explain chloride retention during fever. It must be assumed that the water retained during fever is a cause of the retention of chlorides. During a fever the tissue are more water-logged and their ability to absorb sodium chloride is proportionally increased.

5. This assumption is supported by the comparison of total liquid uptake and excretion which makes it evident that the organism strives to maintain its regulation of body liquids under physiological conditions also under pathological conditions. It keeps the percentage of sodium chloride in plasmatic liquids constantly close to that encountered in physiological NaCl solution. This means that during an attack of pneumonia the amount of water retained by the organism is in proportion to the NaCl retained, corresponding to a physiological sodium chloride solution.

6. In abdominal typhus sodium chloride retention can be observed up to the time when temperatures finally decline. In the beginning of the fever-free stage (in my case on the fourth day) excretion is insignificantly increased. But from then on I found retention even as late as on the 13th fever-free day. The gradual increase in excretion starts with the first fever-free day -- and, together with a considerable increase in the amount of urine excreted, may last for two to three weeks. At a time when nourishment is ample NaCl content of the urine fluctuates between 20-25 g. The respective quantitites of water and NaCl retained are in the same proportion here as in pneumonia patients.

7. In malaria, chloride metabolism is changed in the opposite direction from its change during pneumonia or typhus. On the day of the fever attack a quotidian malaria patient excretes more NaCl in the urine portion collected during the fever attack than he has ingested, while there is a sodium chloride retention during the fever-free interval. Regular urine analyses performed every two hours yielded the result that its NaCl content gradually increases with a rise in temperature. At the peak of the fever more NaCl is excreted than during the first period of temperature decline even though the quantity of urine excreted is smaller during the former than during the latter. P_2O_5 excretion runs an opposite course. It is at a low at the peak of the fever, and increases gradually as temperatures decline. The portion of urine collected during the attack of fever is larger than that before or after the fever. This was also shown in a case of quartan fever in that the quantity of urine collected during 24 hours on the day of the fever exceeded the daily norm, while the quantity collected on fever-free days was usually somewhat below the norm.

8. This paradoxical behavior of NaCl excretion in malaria patients is the result of increased erythrolysis. This is further indicated by the fact that urine excreted during a fever attack, and even more so the feces, contained more than the normal quantities of urobilin.

9. NaCl retained during the fever-free interval is used for the reconstitution of red blood cells which have disintegrated during the fever.

10. Resorption of NaCl did not differ from physiological conditions during attacks of pneumonia, typhus or malaria; the feces always contained little NaCl. But none of the patients participating in the investigation suffered from nethritis or edema.

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