

From the Children's Hospital in the Hufeland Hospital Berlin-Buch (director: Professor Dr. H. Kirchmair)

Treatment of Hepatitis epidemica in Childhood with High Doses of Ascorbic Acid

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With 5 text figures

During recent years the number of cases of hepatitis epidemica has increased quite considerably. The number of referrals to our children's hospital rose thus from 12 in 1953 to 166 in 1956 (fig. 1). Since in the GDR hepatitis epidemica is one of the mandatorily notifiable illnesses, it is us possible for us to show its increase in this district using figures gathered by the Ministry of Public Health; we see (fig. 2) that the number of illnesses rose from 789 cases in 1951 to the enormous number of 29,896 in 1956. Although the number of fatalities did not rise as strongly (fig. 3), there is nevertheless some cause for concern just as with the increase in illness cases.



Fig. 1. Patients treated for Hepatitis epidemica at Children's Hospital

Berlin-Buch

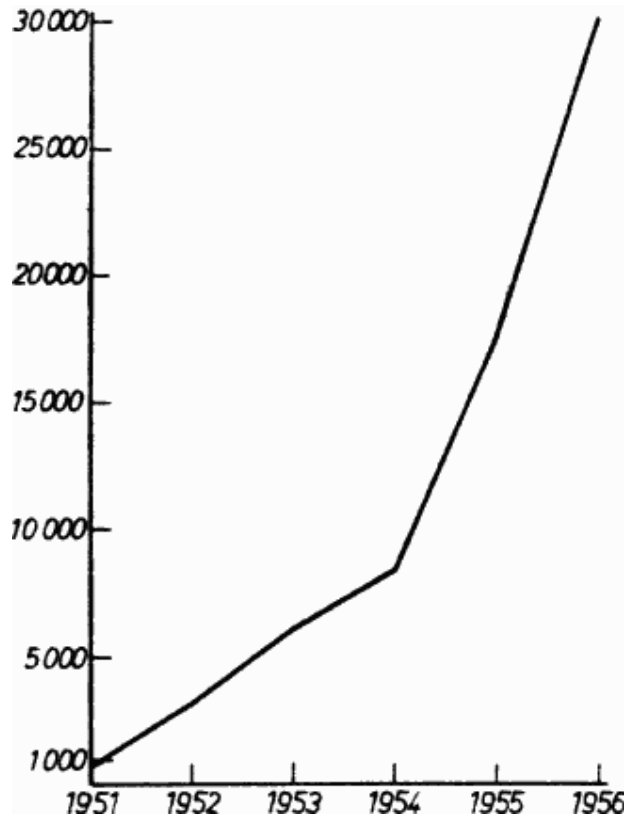


Fig. 2. Merged Hepatitis epidemica Patients in the DDR (excluding Berlin)

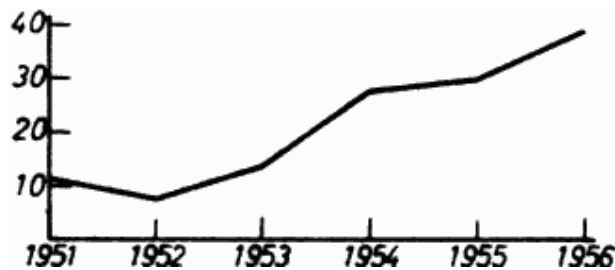


Fig. 3. Merged Mortality due to Hepatitis epidemica in the DDR (excluding Berlin)

Even if, by obligation, registration of more disease cases is more assured in our district, an increase in new illnesses for a long time has nevertheless also become apparent in the domain of the Federal Republic [BRD], as was shown by *Jacobi*, and also found by *Curtius*, *Grühn* and *Wilckhaus* with the illness cases of children.

With an illness, increasing in such an alarming manner, which first of all is not to be healed in few days or weeks and which not rarely leads additionally to recidivism or life-endangering complications, secondary illnesses or organ alterations, one is compelled to reexamine which medical tools for hepatitis therapy — symptomatic and specific — are at our disposal. Already the myriad recommendations for treatment shows us that we are still far distant from an even somewhat effective therapy. Already tried earlier is treatment with insulin with simultaneous administration of glucose (*Guenkin et al*), which they continue to recommend. The combination of insulin-grape sugar [dextrose] with calcium gluconate, suggested by *Hempson*, did not result in improvement in efficacy. *Graff* tried, with Aureomycin, Chloromycetin or, by a combination of these antibiotics with Cortiron, to shorten hepatitis epidemica. Successes were not by any means convincing. Later *Beckmann*, *Müller* and *Wiedenmann* expressly determined that treatment with Aureomycin cannot achieve a shortening of the disease duration, and that this antibiotic therapy might be recommended at best in the initial stage of hepatitis epidemica.

The treatment that over the course of time has shown the most favourable results, was up to now one adjusted according to disease status: diet, administration of choline chloride, methionine or preparations combining these two; furthermore, vitamin B complex, vitamin C (about 150 mg daily) and possibly Decholin, Hepatrat, as well as levulose preparations et cetera. *Heller-Krause* rightly refers to the danger of overdosing only one amino acid, which can lead to correlation disturbances in protein metabolism.

The fact that the use of high-dosage vitamin B₁₂ in hepatitis epidemica has no influence on the course of the illness, could substantiate *Campbell* as well as *Still* and *Wachter*.

In 1952 *Magerl* proposed a treatment of children with hepatitis epidemica with Percorten. *Grund* reported better results by administering Pancortex, which, besides fresh glandular extract, contains ascorbic acid; and which supplies the patient in the indicated dosage not only adrenal cortex extract but also 500 mg vitamin C daily. It is worth mentioning in this context a report by *Wildhirt*, which twice observed liver fattening after cortisone treatment of hepatitis epidemica. More recently *Siede* and *Klamp* tried a treatment of mild and serious viral hepatitis with Prednisone (Decortin). Over ten days they administered a total of 250 mg to 30 patients according to an assigned schedule. A similarly sized control group was treated as usual with levulose, glucose, Pancortex, choline, vitamin B complex and vitamin B₁₂. Dietary treatment was the same with both groups. Within the first 2-3 days of Prednisone therapy the general condition improved very impressively. After 5 days the bilirubin status was around 52.8%; at the 11th day, around 69% of the initial value. The corresponding values of the control group's amounted to 15% to 37%. Likewise the test results of bilirubin excretion, Takata-reaction and the thymol turbidity test displayed more favorable progress with the Prednisone group.

To the authors the therapeutic effect of Prednisone thus seemed confirmed. But it must nevertheless be pointed out that, in one instance, genuine recidivism occurred with a prednisone treated patient; and that twice, with early administration of prednisone, the patients again became icteric.

To point out the multiplicity of therapy attempts, the following should be mentioned: *Schliephake* reported a treatment of hepatitis epidemica with microwaves (ultra-shortwave with a wavelength under 1 m and a frequency of 300 MHz). On the other hand *Braeuker* recommends a sympathikus-therapy of paravertebral anaesthesia of the liver segments D7 to D9, as was suggested years ago by *Nonnenbruch*. Beyond that was recommended an early injection into the right ganglion coeliacum and into the following right ganglia of the plexus coeliacus.

A surprising success in the treatment of hepatitis was had by *Baur* and *Staub* (1954), who gave 11 patients high doses of Redoxon, namely daily intravenous infusions of the 11 with physiological saline solution with a content of 1% ascorbic acid. But in 1956 *Staub* then admitted in passing at the Freiburger Symposium "Pathology, Diagnosis and Therapy of the Liver Diseases" that reexamination in alternating series would have shown that, with this therapy as well, success in shortening illness could not be assuredly achieved.

Stockmann administered less vitamin C; namely to children he gave, besides artificial Carlsbad salts, fat-free food and warmth, up to 500 mg Cebion daily. In more than 100 cases of epidemic hepatitis it could be demonstrated that only a few days after beginning treatment the general state improved, the patients regained appetite, and the previously very dark urine became brighter.

Although the literature indicated inconsistent success in the ascorbic acid treatment of infectious hepatitis, we were prompted to likewise try a treatment with more highly proportioned doses of vitamin C. Initially we gave drip infusions with 5 g ascorbic acid daily to the sickened children, but saw thereby however no marked improvement of the course of the hepatitis, and also observed sporadic recidivism with this dosage.

In order to weaken the argument that the infusion of larger quantities of liquid per se be substantially involved in the success of the hepatitis treatment, we gave a set of children 1000 ml daily drip infusions of equal parts isotonal and saline solution. *Gutzeit* had already suggested that the administration of large quantities of liquid favors the healing process in hepatitis by the removal of toxic metabolites. However, we could confirm no effect and again observed occasional recidivism.

We saw a clear and substantial improvement compared to to all prior treatment methods only when we gave about five-day-long daily drip infusions with 10 g ascorbic acid* in 100 ml water added to 500 ml 0,9% saline solution, as well as 400 ml Isotonal IV (after *Baur* and *Staub*).

[* The substantial quantities of ascorbic acid were placed at our disposal by the German Hoffman La Roche AG, Grenzach/Baden (Redoxon), and by Jenapharm, Jena.]

All patients were treated as follows: strict bed rest, dry wrappings over almost the whole trunk, vitamin B complex, and a fat-free, carbohydrate- and protein-rich diet. Addition of [dietary] fat occurred only after complete alleviation of liver swelling and disappearance the gall pigments from the urine. Additionally, up to the beginning of the ascorbic acid treatment we gave the medicaments choline chloride, methionine and magnesium sulfate.

With a total of 63 patients the indicated basic treatment was maintained; however the medicamental therapy was replaced by drip infusions with vitamin C. 15 children were treated with vitamin C according to the severity of their illness; as with the control group, they received the additional medicaments indicated above.

With children over 5 years the infusion solution altogether comprised 1000 ml as follows:

100 ml 10% ascorbic acid solution,
500 ml 0.9% sodium chloride solution,
400 ml Isotonal **.

** Isotonal is comprised as follows: 0.1% dextrose, 0.8% sodium chloride, 0.04% potassium chloride, 0.25% calcium chloride, 0.0005% magnesium chloride, 0.001% sodium phosphate and 0.05% sodium carbonate.

Children under 5 years received half of the indicated quantity as continuous drip infusion. According to the lowering of serum bilirubin as well as the decrease of the gall pigments in the urine, the intravenous infusion was given over 4-8 days.

In order to convince ourselves whether the method of application of vitamin C is important for success, we proceeded to give the indicated infusion liquid as a rectal drip infusion to a series of children. In some cases, because of bad veins or due to moderate irritation symptoms at the [intravenous] insertion site, we had to resort to combined intravenous-rectal application. After changing over to this method and with applying "Thrombophobe" salve to the insertion sites and environs, the said irritation symptoms did not recur.

The rectal drip infusions were given to the various patients over 5-10 days; we gave the combined intravenous-rectal drip infusion for 6-8 days, depending upon the investigation findings. At a drip rate of 35/min using a DIN-1 cannula, the IV drip infusions took 4-6 hours; the rectal drip infusion, at a drip rate of 40 to 60/min, about 3-4 hours.

As criteria for the duration of the ascorbic acid treatment as well as the further healing process we used: the decrease of serum bilirubin content to normal; the duration of the excretion of bilirubin, urobilinogen and urobilin in the urine; the resolution of the blood corpuscle sedimentation reaction; the decrease the testable liver enlargement and; the evaluation of changes in weight.

Remarkable in the first days were the subjective improvement of the patients, their good appetite and a very good increase in weight, [the latter of] which assuredly was not due to water retention, since in all cases we could observe an excessive diuresis. This diuresis seems to correspond to that which also otherwise often occurs (however much later) during the convalescence of hepatitis, as chloride and the water stored during the preicteric phase are again separated. After *Abbasy, Evans* et al attribute vitamin C, among other things, with a very distinct diuretic effect on hepatic, renal and cardiac fluid retention. However, how this effect comes about is not yet well-known.

The very rapid decrease of liver swelling (fig. 4) was particularly remarkable. Parallel with this decrease of liver swelling is the observation of fading of the icterus of skin and sclera. As earlier, the BSG is likewise clearly more rapidly normalized with the patients treated with vitamin C.

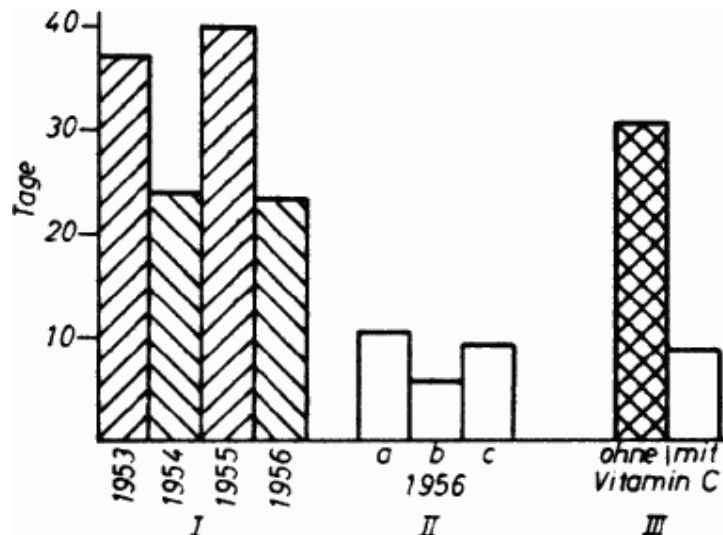


Fig. 4. Decrease of Liver Swelling in Days
I: With Common Therapies in the Years 1953-1956
II: With Treatment with High-Dose Vitamin C
a) intravenous continuous drip infusion
b) rectal continuous drip infusion
c) combined intravenous and rectal
III: Average of I and II

With vitamin C treatment the gall pigments disappeared rapidly from the urine to the rapid fading of the icterus and the decrease of liver swelling.

These patients could be loaded with fat throughout the second week. The transition to higher-fat food was handled well, there was no recurrence of gall pigments in the urine, and we saw no recidivism with the patients treated with high-dose vitamin C.

With our ascorbic acid-treated children we also presently observed after the first days that no further head, muscle or joint pain occurred; additionally, the formerly frequently-observed Herpes labialis no longer occurred. Also furunculoses, which formerly were not uncommon, now did not occur with our patients.

If we now compare the duration of clinical treatment with common therapies, as were conducted here in the years 1953-1956, to the treatment with high vitamin C administration, an impressive difference (fig. 5) results. Whereas we formerly needed on the average 64.9 treatment days until we could discharge the patients as healed, with our 63 patients who received high-dose vitamin C, it now took just 31.8 days. No significant difference exists between the three different methods of application of ascorbic acid (intravenous, rectal, combined intravenous-rectal).

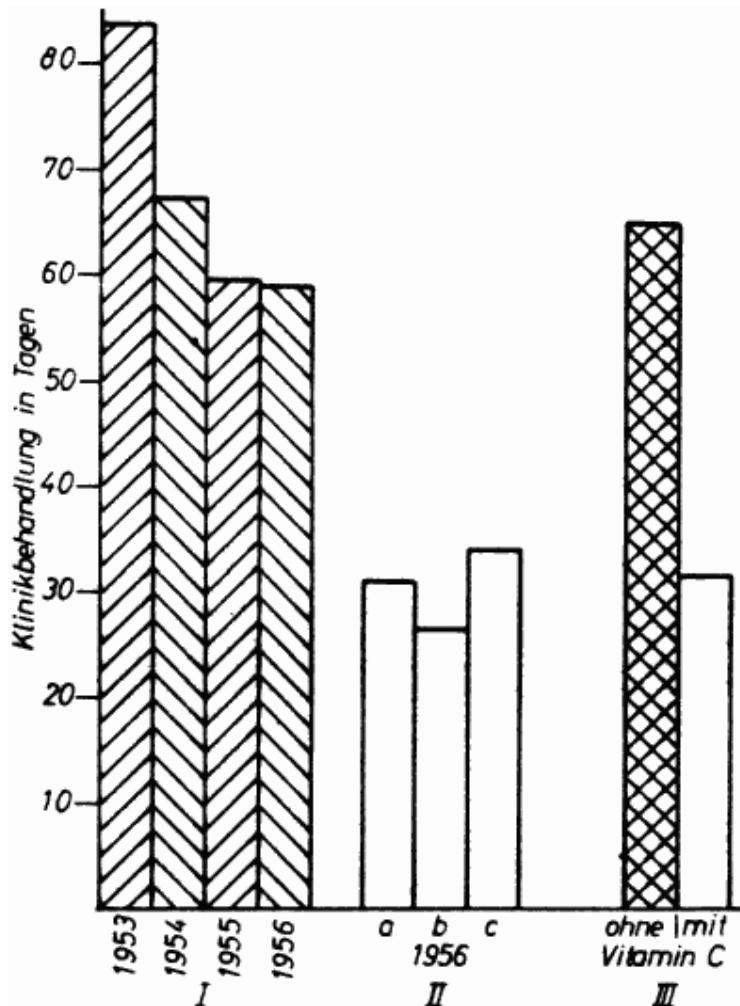


Fig. 5. Clinical Treatment in Days

I: With Common Therapies in the Years 1953-1956

II: With Treatment with High-Dose Vitamin C

a) intravenous continuous drip infusion

b) rectal continuous drip infusion

c) combined intravenous and rectal

III: Average of I and II

In order to estimate the absorption of the ascorbic acid with different applications, we determined the vitamin C content in 24-hour urine with Dichlorphenolindophenol titration according to *Tillmans*. If the patients had formerly been medicated with the usual therapy, then the result was a daily elimination of approximately 20 mg ascorbic acid on average. This contrasts with the children kept on intravenous ascorbic acid, 10 g daily, who excreted a further 200-300 mg daily ascorbic acid.

This was after an initial increase of vitamin C elimination of up to 90% of the infused quantity during the infusion period (after issuing the Vitamin c supply), which was long followed with continuous food for 14 days. If the patients received the 10 g ascorbic acid by means of rectal drip infusion, then no increased initial elimination occurred, but rather immediately about 200-300 mg ascorbic acid were daily excreted in the urine. (This difference of the absorption and the elimination by the kidney is at present the subject of a detailed investigation.)

|* the 2,6-Dichlorophenol-indophenol was provided us by E. Merck, Darmstadt. |

With our patients we could not observe the dyspepsia, the sleeplessness as well as an increased agitation, described by *Rietschel*, as he witnessed with healthy children with overdoses of vitamin C.

After *Stepp, Kühnau* und *Schroeder*, ascorbic acid is practically innocuous; any surplus is excreted. Doses which contained the 1000-fold their daily requirement were tolerated by experimental animals. Recently, humans have received up to 16 g daily, without any toxic effects observed.

It appears to us now with difficulty to find an explanation for the effect of the high ascorbic acid doses in the treatment of hepatitis epidemica. After *Lehnartz*, the biological function of ascorbic acid is based on its characteristic as a redox system, among other things; however, it appears very doubtful that that the simple redox effect is of concern here. If this were the case, then for example the appropriate Zysteingaben [cyst-application] must have the same influence on the course of hepatitis epidemica, which, however, — as we tested — is not the case. One could instead assume that the stimulating effect of ascorbic acid plays a role in the process of complement- and antibody-formation (see *Stepp, Kühnau, Schroeder*). It appears more probable to us, by the diuretic effect of ascorbic acid with hepatitis, among other things, that an activation of adrenal cortex incretion is involved in the effect. The fact that a lack of ascorbic acid exists with hepatitis epidemica has been repeatedly determined (*Tomaszewski, Pennetti* and *De Ritis, Galvan, Gounelle* and *Marche*). A lack of vitamin C can again cause a malfunction of the adrenal gland. Through assorted stimuli of specific or nonspecific types (Stress), a HVL-NNR mechanism is set in motion, and with it a vigorous release of ACTH and Cortison [cortisol]. The Honnon Overproduction lowers the vitamin C status in the blood still further and leads finally to a disappearance of the vitamin from the adrenal gland (*Schroeder*). *Ferstl, Heppich* and *Schmid* also pointed out that the refractory phase of the ACTH is absent during simultaneous ascorbic acid administration; they posited therefore a replenishment of the organ's reserves with vitamin C, in order to prevent increased consumption in the adrenal cortex, and thus the ensuing dysfunction. Also presently under investigation are these questions over the participation of the adrenal gland and/or the adrenal cortex hormone with the therapy of hepatitis.

Mention should be made of the investigation of *Klodt*, which demonstrated that gall [bile] is substantially involved with the absorption by vitamin C. Vitamin C deficiency of the patients was worsened still through the lack of vitamin C absorption during the icteric phase.

Ascorbic acid is protective during experimental liver damage (*Hirata, Beyer, Milhorat et al*). *Hirata* obtained an acute liver damage in rabbits by injection of an emulsion of chloroform and olive oil; thereafter followed a drop in the vitamin C content of the blood, the liver and the suprarenal bodies to approximately half of the normal values. After the acute damage a loss of the liver glycogen was also observed. If the rabbits with the liver-damaging injection received at the same time C in high dosage (200 mg per kilogram body weight) to vitamin, then the glycogen content of the liver did not drop. Daily administration of ascorbic acid in same dosage to untreated animals led to a rise of the quantity of liver glycogen around 30%. Histologically, no liver damage could be demonstrated in the animals receiving chloroform and ascorbic acid simultaneously. These investigations speak for the fact that the ascorbic acid is able to eliminate liver dysfunctions. *Burkman* obtained quite similar test results with simultaneous administration of ascorbic acid after intoxications of carbon tetrachloride with rabbits, guinea pigs and such.

Even if we cannot yet explain today the effect of high vitamin C doses with hepatitis epidemica, we nevertheless consider it important to report here since us this therapy seems to be at present the best and most successful.

Over the question of whether, with oral administration of vitamin C in equally high doses, a similar effect can be attained in hepatitis epidemica, we can today answer that this is not the case. Further details on these investigations must wait for a later report.

Summary

We treated 63 children* who had contracted hepatitis epidemica with daily 10 g ascorbic acid in 1000 ml infusion liquid on the average in each case 5 days duration. The method of application (intravenous, rectal, combined intravenous-rectal) did not result in significant differences.

|* the number of the patients treated with ascorbic acid increased meanwhile to over 100; moreover, treatment success was the same.|

Serving as a comparison group, from the years 1953 to 1956, 63 hepatitis patients of the same severity were treated with choline chloride, methionine and magnesium sulfate.

In the case of the therapy with high vitamin C doses arose [the following]:

In the first days a marked subjective improvement presently occurred, as well as good appetite and weight gain. An excessive diuresis was observed.

The liver swelling subsided rapidly. Formerly it took on the average 30.3 days until the liver size was normalized; with ascorbic acid treatment, an average of 8.6 days was the case. With it we saw a simultaneous rapid disappearance of the marked [skin and scleral] jaundice. The transition to fat-richer food was possible throughout in the second week of the treatment; this was well-tolerated without exception. Recidivism or reappearance of biliary substances in the urine were not observed.

Whereas with earlier therapies clinical treatment lasted an average of 64.9 days, we could discharge our patients after only 31.9 days.

Summary

[English version provided in original article]

63 children with epidemic hepatitis were treated with daily doses of 10 g ascorbic acid in 1000 ml infusion fluid for an average period of 5 days. The mode of administration (intravenous, rectal or as a [*sic*: an] intravenous-rectal combination) did not influence the results to a significant extent.

63 patients with hepatitis of comparable severity from the years 1953 to 1956 served as controls; they had been treated with choline chloride, methionine and magnesium sulfate.

Therapy with high doses of vitamin C showed the following effects: Already during the first few days marked subjective improvement was noticed, followed by good appetite and weight gain; excessive diuresis was also observed [*sic*: observed].

The swelling of the liver subsided rapidly. In previous cases it took an average of 30.3 days until the liver regained normal size in contrast to 8.6 days under ascorbic acid treatment. At the same time the jaundice disappeared rapidly.

Fat-containing diet could be started in all cases during the second [*sic*: second] week and was well tolerated without exception. Clinical relapses or re-appearance of biliary substances in the urine did not occur. Whereas with the usual therapy hospitalization lasted an average of 64.9 days, only 31.9 days in the hospital were required for patients of the described series.

Bibliography

- *Baur und Staub*: Schweiz. med. Wschr. 1954, 595.
- *Beekmann, Müller und Wiedenmann*: Dtsch. med. 1954, 271.

- *Beyer*: Arch. intern. Med. 71, 315 (1943)
- *Braeuer*: Hippokrates 1953, 712.
- *Burkman*: Klin. Med. (Moskau) 32, 37 (1954).
- *Campbell*: Amer. J. Med. Sc. 224, 252, 1952.
- *Curtius, Grün* und *Wilckhaus*: Med. Klin. 1952, 336.
- *Ferstl, Heppich* und *Schmid*: Wien. Klin. Wschr. 1951, 28.
- *Galvan*: J. Amer. Med. Ass. 114, 2601 (1940).
- *Gounelle* und *Marche*: C. R. Soc. Biol. (Paris) 137, 735, (1943).
- *Graff*: Dtsch. med. Wschr. 1951, 1823.
- *Grund*: Ärztl. Praxis 1951, 4.
- *Guenkin*: Pediatr. 1939, heft 9/10.
- *Gutzeit*: Münchn. med. Wschr. 1950, 29.
- *Hampson*: Brit. med. J. 1931, 3698.
- *Heller-Krause*: Klin. Wschr. 1951, 75.
- *Hirata*: Orient. J. Dis. Infants 21 (1937). ref. Zbl. Kinderheilk. 34, 531 (1938).
- *Jacobi*: Dtsch. med. Wschr. 1950, 1323.
- *Klodt*: Zit. nach *Stepp, Kühnau, Schroeder* l. c.
- *Lehnartz*: Einführung in die chemische Physiologie. Springer, Berlin und Heidelberg 1948.
- *Magerl*: Med. Klin. 1952, 285.
- *Milhorat* et al.: Proc. Soc. exp. Biol. (New York) 45, 394 (1940).
- *Nonnenbruch*: Ärztl. Wschr. 1947, 1089.
- *Pennetti* und *De Ritis*: Rif. med. 55, 1383 (1939).
- *Rietschel*: Klin. Wschr. 1939, 923.
- *Schliephake*: Med. Heute 1955, 245.
- *Schroeder*: Münch. med. Wschr. 1952, 339.
- *Siede* und *Klamp*: Wiss. Z. Karl-Marx-Univ. 4, Math.-naturw. Reihe. H. 5.
- *Staub*: 4. Symposium „Pathologie. Diagnostik und Therapie der Lebererkrankungen“, Freiburg v. 29. 6. 1955.
- *Stepp, Kühnau, Schroeder*: Die Vitamine und ihre klinische Anwendung. Ferdinand Enke, Stuttgart 1957.
- *Stille* und *Wachter*: Ärztl. Wschr. 1954, 129.
- *Stockmann*: Ärztl. Praxis 1955, 9.
- *Tomaszewski* Pol. Gaz. lek. 1936, 756.
- *Wildhirt*: Med. Klin. 1955, 713.

Anschrift der Verfasser: Berlin-Buch, Kinderkrankenhaus im Hufeland-Krankenhaus.

Aus *Medizinische Monatenschrift*, 11 Jahrgang, Heft 6, 1957.

[Note: This was an extremely difficult translation; the original contained unusually convoluted phrasing and syntax. Clarifying insertions have occasionally been added [thus].

Several typographical/grammatical errors in the English abstract were noted and have been marked with [sic]- AscorbateWeb Editor]

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