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SERUM TRANSAMINASE ACTIVITY AND LIVER ALTERATIONS IN BRONCHIAL ASTHMA

By

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The greatest increases in serum glutamic oxaloacetic and glutamic pyruvic transaminases (SGOT and SGPT) presumed to reflect tissue damage, are observed in cardiac, hepatic and muscular diseases (see *Wroblewski* (17)). On the other hand, *Colldahl* (4) and *El-Shaboury et al.* (6) noticed increased serum transaminase values in patients with severe bronchial asthma and status asthmaticus.

We have tried to correlate the serum transaminase activity in asthmatics to the arterial carbon dioxide tension and oxygen saturation and both to the clinical picture. In some cases liver morphology (biopsies) was also studied.

MATERIAL AND METHODS

The material comprises 317 asthmatics warded during one year at the Hospital for Allergic Diseases and admitted during a severe stage of the disease. Patients with signs of myocardial damage, heart failure and primary liver or biliary diseases were excluded. The age of the patients varied from 15 to 77 years.

Serum transaminases and blood gases were determined on admission and several times during the stay in hospital. The SGOT and SGPT were determined colorimetrically (13), the carbon dioxide tension by the Astrup micro-method (15) from fingertip arterial capillary blood and the oxygen saturation by ear oximetry with an Atlas oximeter.

Th liver biopsies were taken by means of 1.2 or 1.8 mm Menghini (8) needles, fixed in 10 per cent formalin and embedded in paraffin. The first report on

the biopsies in most cases was given on hematoxylin-van Gieson stained sections. Later from all cases 6 μ m serial sections were stained with H&E, Schiff's reagent after oxidation with periodic acid with and without preceding digestion with saliva for the removal of glycogen, with Wilders reticulin stain and with the Turnbull blue reaction for iron. Unfortunately lesions present in the first sections seldom were seen in the final serial sections.

RESULTS

The SGPT was increased in 35 patients out of 317 (16 males, 19 females age 24-76 years), *i.e.* in 11 per cent. Very high SGPT values (over 300 units/ml) were found in six patients. In one subject the SGPT activity was 2420 units/ml.

The SGOT activity was increased in 15 subjects, the highest value being 775 units/ml. As a rule the SGOT activity paralleled the SGPT activity. In some cases with a slight elevation in the SGPT, the SGOT was, however, within normal limits. (Table 1).

TABLE 1
Serum Transaminase Activity in 317 Asthmatics.

SGPT	No. of patients	SGOT	No. of patients
< 40	282	< 40	302
40- 70	16	40- 60	5
71-300	13	61-100	7
>300	6	>100	3
	35 35		15 15
	317		317

TABLE 2
Peak SGPT-Activity in 35 Asthmatics.

Time in Hospital	No. of patients
1- 7 days	15
8-21 "	13
22 "	7

TABLE 3
*Carbondioxide Tension and Oxygen Saturation in 15 Patients
 in Status Asthmaticus.*

SGPT	PCO ₂ mmHg	O ₂ sat %
< 40 (n = 7)	41.9 ± 5.48	75.6 ± 5.83
> 40 (n = 8)	41.6 ± 4.80	83.1 ± 7.24

TABLE 4
*Carbon Dioxide Tension and Oxygen Saturation in 317 Asthmatics grouped
 According to Level of SGPT-Activity.*

SGPT	PCO ₂ mmHg	O ₂ sat %
< 40 (n = 282)	42.4 ± 4.2	78.6 ± 9.4
41-70 (n = 16)	42.8 ± 3.08	82.4 ± 5.74
71-300 (n = 13)	43.5 ± 6.16	80.0 ± 14.9
> 300 (n = 6)	43.0 ± 5.34	73.5 ± 7.04

Although the patients were admitted to hospital during a severe period of the disease, the highest serum transaminase activity (STA) was not always found on admission. In 15 subjects the peak was noted during the first week, in 13 during the next two weeks, and in 7 unexpected elevations were noted after three weeks' treatment (Table 2). Seven subjects were warded 3 times and five subjects twice, in these the STA was not at the same level each time; only three had elevated STA on subsequent admissions.

15 subjects were admitted to hospital in status asthmaticus; elevated STA was observed in 8 of these (Table 3). Several of the 35 subjects with elevated STA had a slight hypercapnia

and a slightly decreased arterial oxygen saturation, estimated at the time of the STA determination. The mean values of the carbon dioxide tension and oxygen saturation did not, however, differ significantly from those of the subjects with normal STA (Table 4).

In the following cases liver biopsy was performed.

Case 1. AR. Female, 55 yrs.

Two years history of bronchial asthma. Admitted to hospital in severe respiratory distress. On auscultation rhonchi over both lungs. BP 165/100, pulse rate 85/min. The liver was not enlarged; no peripheral oedema. Chest and sinus X-ray normal. ECG showed right axis deviation. Laboratory findings: SR 12, Hb 13.0 g/100 ml, Er, 4.34, Leuc 6.800, Eos 330/ μ l, Alkaline phosphatase 1.45 B-L units. BSP retention 7.1 per cent in 45 min. Acid-base status: pH 7.45, PCO_2 38 mmHg, $\text{BE}+$ 2.2 mEq/l, O_2 saturation 86 per cent., SGOT 51-35 and SGPT 79-41¹. No exogenic allergens were found.

The patient remained at the hospital for 13 weeks and was discharged well.

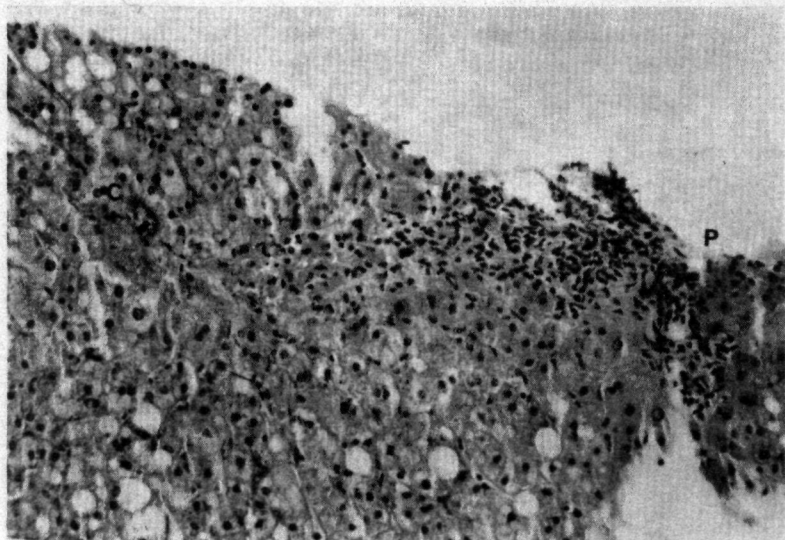


Fig. 1.

Case 1. The inflammatory infiltrate in the portal tract to the right as a band of degenerated cells and some neutrophils seems to extend towards the central vein to the left. Hematoxylin-van Gieson. $\times 240$.

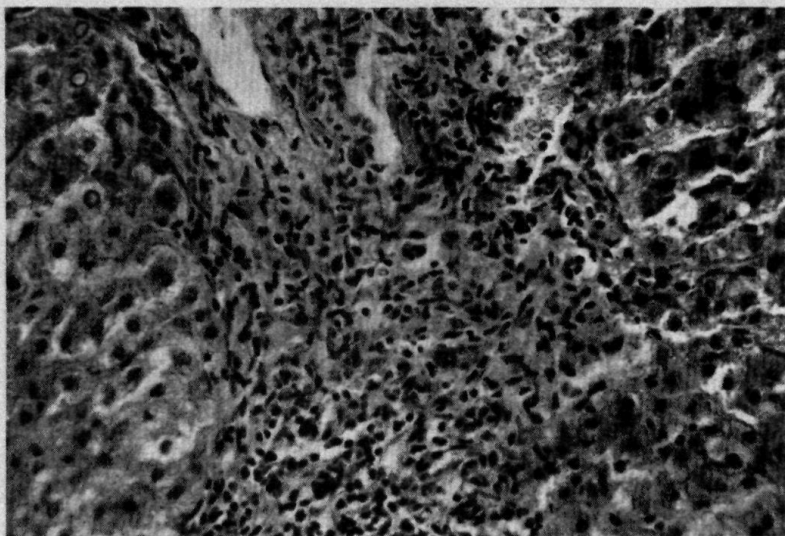


Fig. 2.

Case 2. Lymphocytes and macrophages dominate in this lesion adjacent to a portal tract. Haematoxylin-van Gieson. $\times 375$.

She was treated with chloramphenicol, tetracyclines, erythromycin, sulfonamids, bronchodilators, imipraminechloride, Entoral, Trichomycin and vitamins. Two days prior to liver biopsy, which was performed at a second admission 2 months later, the SGPT was 41.

Microscopy: In one of the pieces normal liver cells have disappeared from a bandlike area which seems to extend from a portal tract towards a central vein (Fig. 1). Some of the cells with dark nuclei seem to be degenerating liver cells, between these there are neutrophils, lymphocytes and phagocytes. Part of the circumference of the vein is unaltered. Some other apparently similar small foci are seen. Two rather homogenous, acidophilic bodies, one with a pyknotic nucleus, were seen. In other parts of the liver there seems to be an abundance of Kupffer cells containing saliva-resistant, PAS-positive granules. Some liver cells seem hydropic, a light fatty vacuolation is present.

Case 2. ET. Female, 51 yrs.

Treated in hospital because of pulmonary eosinophilia ten years ago, had asthmatic distress since then. Admitted to hospital for examinations in rather severe respiratory distress; physical examination revealed rhonchi over both lungs. BP 120/90, pulse rate 110/min. X-ray showed pansinusitis and some fibrotic streaks in both lungs. ECG normal.

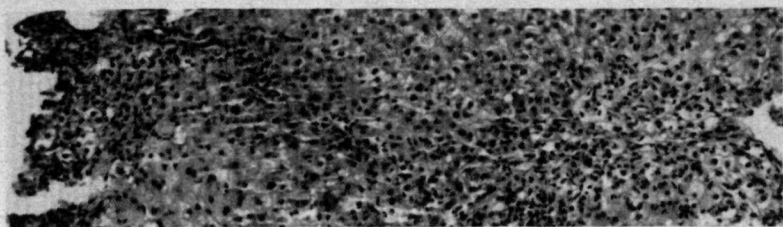


Fig. 3.

Case 2. Except for a small gap the band of degenerated liver cells and inflammatory and phagocytic cells extends from the portal tract (left) to the central vein (right). Hematoxylin-van Gieson. Panorama micro photography diminished to about one third from original enlargement of $\times 375$.

Laboratory findings: SR 5, Hb 14.4 g/100 ml, Er 4.86, Leuc 8.700, Eos 1230/ μ l, BSP 11.6 per cent retention in 45 min., Acid-base status: pH 7.44, PCO₂ 40.0 mmHg, BE+ 2.9 mEq/l, O₂ saturation 85 per cent, SGPT 83 - 54-39. No exogenic allergens were found.

The patient was treated with tetracyclines, Trichomycin, corticosteroids, bronchodilators, Librium and vitamins. The liver biopsy was performed on the fourth day of hospitalization, 2 days earlier SGPT was 83.

Microscopy: There are many foci containing inflammatory cells but no normal liver cells. In some foci granulocytes predominate, in others lymphocytes and phagocytizing cells (Fig. 2). One focus, except for a small gap in the section, connects a portal tract to a central vein as a narrow band (Fig. 3). Most foci, however, are adjacent to vessels or located in the intervacular parenchyma. In some foci very thin fibers staining with acid fuchsin are observed. Some liver cells seem hydropic.

Case 3. EH. Female, 40 yrs.

Two years' history of severe asthmatic distress, admitted to the hospital in severe status asthmaticus. The patient was well-nourished but exhausted and profusely sweating with considerable rhonchi over both lungs. Pulse rate 140/min., BP 160/120, normal ECG. Chest X-ray showed no fresh inflammatory process. The mucosa of the nasal sinuses was hypertrophic.

Laboratory findings: SR 10, Hb 16.5 g/100 ml, Er 4.89, Leuc 6.700, Eos 60/ μ l, Alkaline phosphatase 0.95. Acid-base status: pH 7.48, PCO₂ 32.5 mmHg, BE+ 2.0 mEq/l, O₂ saturation 85 per cent. SGOT 406-725-308-65-20-15. SGPT 2420-102-87-23 42-~~530~~-280-58-28.

No exogenic allergen was shown to be present.

The patient was treated in hospital for 8 months during a very severe period

¹ The value in the black type refers to the date after which liver biopsy was performed.

of the disease and she was given corticosteroids, erythromycin, tetracyclines, chloramphenicol, Albamycin, penicillin, Trichomycin, bronchodilators, sedatives and vitamins. Under the corticoid treatment the STA decreased to normal levels. After 4 months' treatment liver biopsy was performed. 2 days earlier the SGPT was 530.

Microscopy: The liver tissue seems almost normal except for some areas where the Kupffer cells seem enlarged and contain saliva-resistant PAS-positive granules. A few small collections of inflammatory cells are seen.

Case 4. EV Male, 24 yrs.

Half a year's history of asthmatic distress, treated in a rural hospital for one month before admission. On admission the patient was in severe respiratory distress, cyanotic and exhausted with rhonchi over both lungs. Pulse rate 130/min. BP 140/95. In ECG negative T waves in left precordial leads (V_2 - V_5). Chest X-ray was normal, while sinus X-ray showed signs of sinusitis.

Laboratory findings: SR 13, Hb 16.4 g/100 ml, Er 5.9, Leuc 11.800, Eos 550/ μ l. SGPT 66-58, GOT 39. Acid-base status: pH 7.42, PCO_2 42 mmHg, BE + 2.3 mEq/l.

The patient was treated with saline infusions, corticosteroids, tetracyclines, Trichomycin, bronchodilators, Librium and vitamins. No exogenic allergen was found. Liver biopsy was performed ten days after admission, 4 days earlier the SGPT had been 58.

Microscopy: Rather normal-looking liver tissue, possibly with a slight increase of PAS-positive, saliva-resistant granules in the Kupffer cells, some of which also give a faint reaction for iron.

Case 5. LV. Male, 48 yrs.

Two years history of bronchial asthma. Admitted to hospital in status asthmaticus, profusely sweating, exhausted and with rhonchi over both lungs. Pulse rate 120/min. BP 170/110, ECG normal. Sinus X-ray revealed mucosal hypertrophy, chest X-ray a light interlobular pleural thickening.

Laboratory findings: SR 15, Hb 14.5 g/100 ml, Er 4.50, Leuc 9000, Eos 1250/ μ l. GPT 62-49-43. Acid-base status: pH 7.42, PCO_2 43 mmHg, BE + 2.6 mEq/l. O_2 saturation 80 per cent. BSP retention 17.4 per cent in 45 min.

The patient was treated with parenteral infusions, corticoids, tetracyclines, Librium, broncholytics and vitamins. In accordance with the results of the skin tests hyposensitisation to house and textile dust was performed. On the day following admission to the hospital the SGPT was 62; liver biopsy was taken 3 days later.

Microscopy: A moderate, apparently central and midzonal fatty vacuolation is the most prominent alteration. A focus of lymphocytes and histiocytes is present at the edge on one section. There may be a slight increase in number of Kupffer cells.

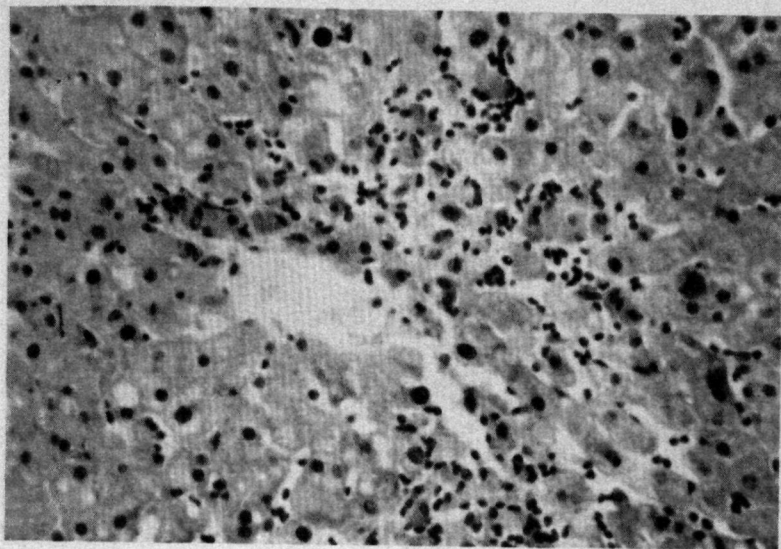


Fig. 4.

Case 7. Degenerated liver cells and inflammatory reaction adjoining a central vein. The lesion does not encircle the central vein completely. H & E. $\times 375$.

Case 6. ET. Male, 24 yrs.

Bronchial asthma since childhood. During the last two months warded twice at a rural hospital for status asthmaticus. The patient was admitted for further examinations. On admission he had moderate respiratory dyspnoea and rhonchi over both lungs. Pulse rate 88/min., BP 170/110, ECG within normal limits. X-ray of chest was normal, the mucosa of the nasal sinuses was hypertrophic.

Laboratory findings: SR 1, Hb 16.3 g/100 ml, Hkr 47 vol. per cent, Leuc 7100, Eos 570/ μ l. Alkaline phosphatase 1.79 B-L units. Acid-base status pH 7.35, PCO_2 38.5 mmHg, BE -3.9 mEq/l, SGPT 122-790-560-280-60, SGOT 38-138-95-55-20.

The treatment consisted of corticoids, tetracyclines, chloramphenicol, bronchodilators, Librium and vitamins. Hyposensitisation to horse epithelium was started after a positive inhalation test. Liver biopsy was performed two weeks after admission, two days earlier the SGPT was 560.

Microscopy: A few small inflammatory foci with neutrophils and a slight general prominence of Kupffer cells containing saliva-resistant, PAS-positive granules constitute the principal findings in the small biopsy.

Case 7. MH. Male, 27 yrs.

One year's history of severe asthmatic distress, admitted to hospital in status asthmaticus with rhonchi over both lungs. Pulse rate 120/min., BP 180/80,

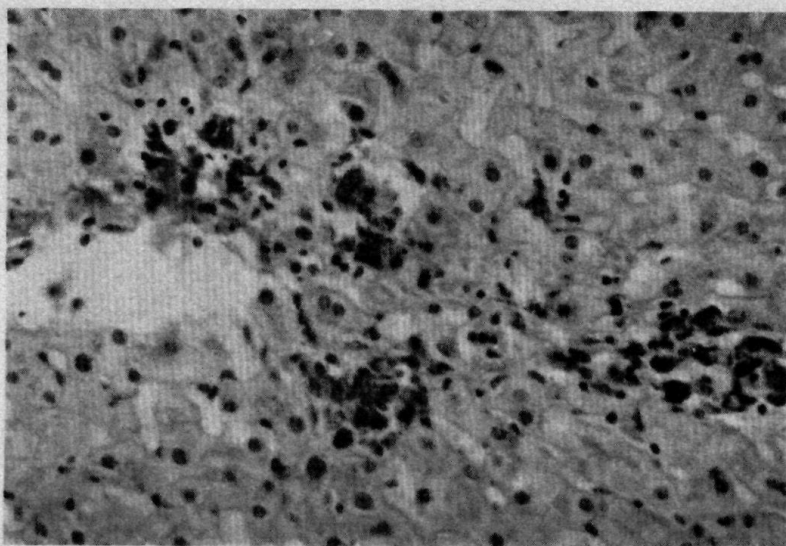


Fig. 5.

Case 7. Same lesion in Fig. 4 in parallel section stained with PAS after digestion with saliva. $\times 375$.

ECG within normal limits. There was some increase in bronchovascular markings around both hila on chest X-ray, nasal sinuses showed signs of mucosal hypertrophy. A duodenal ulcer was revealed roentgenologically.

Laboratory findings: SR 4, Hb 15.4 g/100 ml, Er 4.94, Eos 360/ μ l. Alkaline phosphatase 1.30 B-L units. Acid-base status: pH 7.41, PCO_2 38 mmHg, BE -0.2 mEq/l, oxygen saturation 71 per cent. SGPT 70-100-145-252-~~560~~-470-420-225-90. SGOT 31-70-89-93-70-36.

The patient was treated with tetracyclines, chloramphenicol, Trichomycin, bronchodilators, corticosteroids, Librium and vitamins. Hyposensitisations to lamb wool and house dust were performed in accordance with the result of the skin tests. The liver biopsy was taken on the 11th week after admission, the SGPT 2 days earlier having been 560.

Microscopy: In the small pieces of liver there are many small focal degenerations, most of them radiating from central veins without encircling them completely (Fig. 4). The foci contain cells with rather abundant cytoplasm with light brown granules and small but not always pycnotic nuclei and contain abundant saliva-resistant PAS-positive granules (Fig. 5). Some, though apparently not all of these cells also gave a positive iron-reaction. In most foci these cells seem to be phagocytic. However, the possibility still remains that some may be degenerated liver cells. In addition to these cells there are in

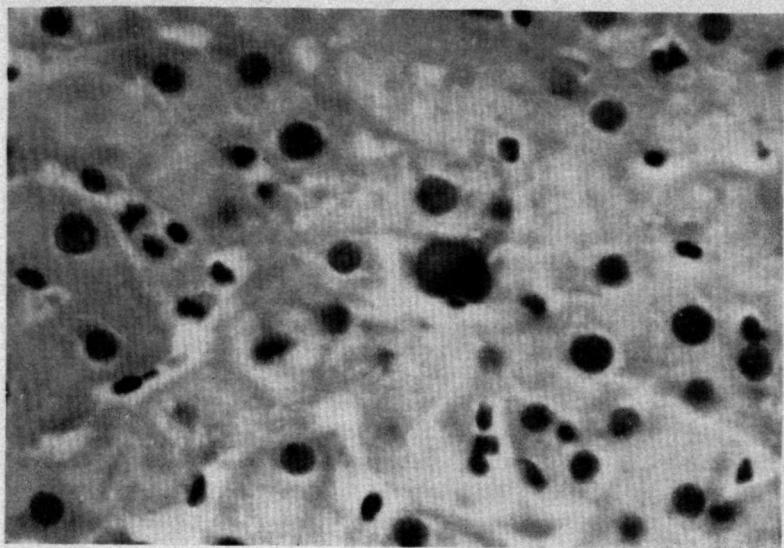


Fig. 6.

Strongly eosinophilic cell with a pycnotic nucleus corresponding to an "acidophilic body". H & E. $\times 900$.

most foci, neutrophils and lymphocytes and fairly numerous erythrocytes. Close to some foci there are a few strongly eosinophilic cells with pycnotic or fragmented nuclei (Fig. 6). The rather strong general pericanalicular pigmentation of the liver cells was PAS-negative. A number of mitotic figures are seen among the liver cells.

Case 8. AN. Female, 60 yrs.

Half a year's history of respiratory distress. At admission to hospital after two months of asthmatic attacks the patient was nervous, anxious, pale, with rhonchi over both lungs. ECG was normal. Chest X-ray showed fibrotic markings. Sinus X-ray was normal.

Laboratory findings: SR 15, Hb 15 g/100 ml, Er 5.31, Leuc 7.700, Eos 970/ μ l, Alkaline phosphatase 1.70 B-L units. SGPT 60-370-~~220~~-120-45-30. SGOT 36-97-51-23. Acid-base status: pH 7.42, PCO_2 43 mmHg, BE + 3 mEq/l. Oxygen saturation 62 per cent. No exogenic allergen was found. She was treated with tetracyclines, chloramphenicol, penicillin, Trichomycin, bronchodilators, Librium, corticoids and vitamins. The liver biopsy was taken five weeks after admission, the SGPT having been 220 a day earlier.

Microscopy: There are a few scattered very small foci mainly consisting of cells with PAS-positive, saliva-resistant cytoplasmic granules, apparently Kupf-

fer cells. There is a rather light pericanalicular pigmentation of the hepatocytes. Some liver cells nuclei are vacuolated, some contain PAS-positive and saliva-resistant inclusions.

Case 9. ES. Male, 70 yrs.

Thirty years' history of asthmatic distress and diabetes mellitus for two years. Well nourished, with some rhonchi over both lung fields, he was admitted to the hospital because of increasing respiratory distress. BP 200/100, pulse rate 60/min., ECG revealed some slight S-T segment depression in bipolar leads I-II.

Chest X-ray revealed moderate increase in perihilar bronchovascular markings, moderate enlargement of the heart and sclerosis of the aortic arch. Sinus X-ray showed some mucosal hypertrophy.

Laboratory findings: SR 8, Hb 16.2 g/100 ml, Hkr 46 vol. per cent, Leuc 6400, Eos 530/ μ l. Alkaline phosphatase 2.20 B-L units. SGPT 38-46-330-480-750-122-90-21. SGOT 27-29-63-104-24-22. Acid-base status: pH 7.42, PCO₂ 41 mmHg, BE+ 2.0 mEq/l. No exogenic allergen was found.

The treatment consisted of tetracyclines, penicillin, chloramphenicol, Chlor-tacillin, Trichomycin, Alentin, Cedilanid, Librium, corticosteroids, vitamins. The liver biopsy was performed 5 weeks after admssion when the SGPT was 750.

Microscopy: From one small portal tract in the large piece of liver a few septa radiate encircling a few liver cells. A few Kupffer cells contain saliva-resistant PAS-positive granules. Some liver cell nuclei contain similiary staining inclusions.

DISCUSSION

Clinical and Biochemical Findings

Increased STA activity was found in 11 per cent of the patients. The increase in SGPT in all cases was more pronounced than that of SGOT suggesting liver damage rather than myocardial lesions (17). The parallellism between the STA and the serum ornithine carbamyltransferase in *Coll-dahl's* cases (4) also strongly points to liver injury. Our findings confirm the opinion of *El-Shaboury et al.* (6) that there is but a poor correlation between the clinical severity of the asthma and the STA levels. Since we were not able to demonstrate a clear correlation between alterations of the blood oxygen saturation or the carbon dioxide tension and the STA levels it seems that we may have to look for factors other

than pure hypoxaemia as the cause of the liver lesion. In this respect our findings differ from those of *Refsum* (12) who found in patients with pulmonary diseases a positive correlation between arterial hypoxemia and enzyme activity.

Summary and Type of Liver Lesions

In three out of nine cases there were lesions interpreted as recent necroses, and in 3 cases collections of inflammatory cells, probably reactions to focal necroses. The lesions did not encircle central veins; in some cases they seemed to link portal tracts to central veins as narrow bands. Phagocytic cells, often containing PAS-positive, saliva-resistant material were common, probably reflecting liver cell injury (11). In two cases structures resembling acidophilic or Councilman bodies were seen. Hydropic degeneration was certainly present in some, possibly in many cases, such lesions are, however rather difficult to quantitate. Fatty vacuolation was seen in some cases, though it did not seem to constitute a fundamental alteration. Bile stasis, pronounced chronic inflammatory reaction, evident central congestion or fibrosis were absent.

Although the liver lesions varied in extent it seems that they at least in most cases may have been of a similar type. The differences were probably due to the fact that the biopsies were taken at different stages of development of the lesions, and that the lesions are focally distributed. The lesions may belong to the group occurring in pneumonias, various gastrointestinal disorders, after surgery etc. and designated as non-specific reactive hepatitis by *Popper & Schaffner* (10). Bronchial asthma has not been mentioned among the cases of non-specific reactive hepatitis. (10, 16).

Association Between Liver Lesions and STA

Increased STA levels are frequently found in non-specific reactive hepatitis (16). In general increased levels of SGOT and SGPT are thought to indicate cell damage, usually necrosis. As pointed out by *Henley et al.* (7) the maintenance of

a enzyme gradient between the interior of the cell and the surrounding tissue probably requires energy, and loss of enzyme from a cell may be due to subtle alterations of cell membrane permeability rather than plain necrosis. It is thus possible that the necroses observed may have contributed to the increased serum enzyme levels to a much smaller degree than some other alterations *e.g.* hydropic degeneration, not so easily grasped in the paraffin sections. This might partly explain the rather poor correlation between the liver alterations and the STA levels.

Cause of Liver Lesions

Colldahl assumed hypoxemia to be the cause of the liver lesions in bronchial asthma. This seemed to fit well into the finding of centrilobular necroses in one of his cases (4). This observation was made at autopsy. Centrilobular necroses, however, are very common post mortem, not only in pulmonary insufficiency (12) and right sided heart failure (14), but they also may develop in the agonal state in cases without previous respiratory or circulatory insufficiency (10). On the other hand, lesions limited to the central vein region were not present in our biopsies. In view of this it seems that hypoxemia might not be responsible for the liver damage, and that we should look for other causes of the lesions. Drug-induced liver injury had to be considered, but such medication was, however, avoided in our patients (5). The only ataract used was Librium. Though jaundice has in one case been reported during Librium (Chlordiazepoxide hydrochloride) treatment the connection between Librium and liver damage is doubted by the writer (2).

Bronchial asthma is generally regarded to be mediated by some allergic mechanism. Since, according to *Muller-Eberhard et al.* (9) immune cytolysis mediated by complement is by no means restricted to erythrocytes, and since, as shown by *Apitz* (1) the rabbit liver may react with focal necroses to repeated injections of foreign protein, it is not theoretically impossible

that the lesions in the present material may be caused by some immunological mechanism. It may be mentioned that *Campbell & Garvey* (3) have shown that the rabbit liver plays an important rôle in the retention of antigen. During storage, the antigen becomes altered in some way, being at least 100 times more potent in the Schultz-Dale test than the original antigen. Part of the antigen may be retained as an antigen-antibody complex and after release of the antibody the retained antigen might become available anew. Thus the liver may contain large amounts of potent antigen able to take part in antigen-induced reactions. This suggestion offers possibilities for speculations and investigations on the pathogenesis of allergic reactions.

SUMMARY

Increased levels of serum transaminases were found in 11 per cent of 317 patients with bronchial asthma. There was no clear correlation between the clinical severity of the asthma and the levels of the serum transaminases, nor between the latter and the blood oxygen saturation or the carbon dioxide tension. In 9 cases with increased STA levels liver biopsy was performed. Morphologically lesions in at least 6 biopsies resembled those described as non-specific reactive hepatitis, rather than central congestive or hypoxemic lesions. The pathogenesis of the lesions is discussed.

REFERENCES

1. *Apitz, K.*: Über anaphylaktische Organveränderungen bei Kaninchen. *Virchow's Arch. f. path. Anat.* 289, 46-82, 1933.
2. *Cacioppo, J. & Merlis, S.*: Chlordiazepoxide hydrochloride (Librium) and jaundice: Report of a case. *Am. J. Psych.* 117, 1040-1041, 1961.
3. *Campbell, D.H. & Garvey, J.S.*: The fate of labeled foreign antigens in the livers of normal and immunized rabbits. *Int. Arch. Allerg.* 12, 70-88, 1958.
4. *Colldahl, H.*: Serum enzymes in patients with asthma and emphysema. *Acta Allergol.* 19, 97-102, 1964.
5. *Dölle, W. & Martini, W.*: Zusammenstellung von Arzneimitteln, die Leberschädigung mit und ohne Gelbsucht verursachen können. *Acta Hepato-Splenol.* 11, 355-367, 1964.

6. *El-Shaboury, A. H., Thomas, A. J. & Williams, D. A.*: Serum transaminase activity in status asthmaticus. *Brit. Med. J.* 1, 1220-1223, 1964.
7. *Henley, K. S., Schmidt, F. W. & Schmidt, Ellen*: Newer diagnostic tests in liver diseases. Ed. Popper, H. & Schaffner, F. Grane & Stratton, New York 1961.
8. *Menghini, G.*: One-second needle biopsy of the liver. *Gastroenterology*, 35, 190-199, 1958.
9. *Muller-Eberhard, H. J., Nilsson, U. R., Dalmasso, A. P., Polley, M. J. & Calcot, M. A.*: A molecular concept of immune cytolysis. *Arch. Path.* 82, 205-217, 1966.
11. *Popper, H. & Schaffner, F.*: Response of the liver to injury. In: *Progress* New York 1957.
11. *Popper, H. & Schaffner, F.*: Response of the Liver to injury. In: *Progress in Liver Diseases II* Ed. Popper, H. & Schaffner, F. Grune & Stratton. New York 1961.
12. *Refsum, H. E.*: Arterial hypoxemia, serum activities of GOT, GPT and LDH, and centrilobular liver cell necrosis in pulmonary insufficiency. *Clin. Sci.* 25, 269-374, 1963.
13. *Reitman, S. & Frankel, S.*: A colorimetric method for the determination of serum glutamic oxaloacetic and glutamic pyruvic transaminases. *Am. J. Clin. Path.* 28, 56-63, 1957.
14. *Sherlock, Sheila*: Diseases of the Liver and Biliary System. Blackwell, London 1963.
15. *Siggaard-Andersen, O., Engel, K., Jørgensen, K. & Astrup, P.*: A micro method for determination of pH, carbon dioxide tension, base excess, and standard bicarbonate in capillary blood. *Scand. J. Clin. & Lab. Inv.* 12, 172, 1960.
16. *Steigmann, F., Svanto, P. B., Meister, H. P. & Pamukcu, F.*: Clinical significance of nonspecific (reactive) hepatitis. *Amer. J. Gastroenterology* 44, 129-137, 1965.
17. *Wroblewski, F.*: The clinical significance of transaminase activities of serum. *Amer. J. Med.* 27, 911-923, 1959.

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