*Pharmacology Biochemistry & Behavior*, Vol. 13, Suppl. 1, pp. 31–36. Printed in the U.S.A.

# Effects of Ethanol on Protein Synthesis and Secretion[1]

MARCUS A. ROTHSCHILD, MURRAY ORATZ, JØRG MORLAND, SIDNEY S. SCHREIBER, ALVIN BURKS AND BARBARA MARTIN

*Radioisotope Service, New York Veterans Administration Medical Center, New York, NY 10010*
*Department of Medicine, New York University Medical Center*
*Department of Biochemistry, New York University Dental Center, New York, NY*
*and the University of Tromsø, Tromsø, Norway*

ROTHSCHILD, M. A., M. ORATZ, J. MORLAND, S. S. SCHREIBER, A. BURKS AND B. MARTIN. *Effects of ethanol on protein synthesis and secretion.* PHARMAC. BIOCHEM. BEHAV. **13**: Suppl. 1, 31–36, 1980.—Liver protein synthesis involves a complex series of reactions which is influenced by hormones, nutritional state and general health of an animal. The secretory processes for proteins, such as albumin, also interact with the protein synthetic machinery of the liver. Alcohol may affect synthesis and/or secretion at a number of loci and the mechanism of alcohol's action could depend on the immediate state of the experimental tissue. Ethanol was shown to interfere with albumin synthesis and the effect was shown to differ when livers from fed and fasted animals were compared. The ethanol effects were also dependent on the metabolism of ethanol rather than on the simple presence of this drug. Acetaldehyde decreased albumin synthesis but in a manner which was distinct from the ethanol effect. Acute ethanol administration under the conditions used in our studies had little effect on secretion of prelabeled proteins from hepatocytes. The implications of studies of the effects of ethanol on liver protein synthesis and secretion are discussed.

Albumin    Ethanol    Perfused liver    Acetaldehyde    Polysomes    4-Methylpyrazole

## In Vivo *Protein Turnover: Problems in Interpretation*

Protein synthesis is perhaps the main reason for all cellular activity. Energy as well as various biochemicals derived from intermediate metabolism are utilized for the synthesis of proteins. The proteins are synthesized both for internal consumption by the cell and for export (eg: hormones or the serum proteins). Before turning to the particular topic of the influence of alcohol and amino acids on protein synthesis and transport, one could disgress a bit to try to point out some of the complexities of trying to understand protein synthesis in an *in vivo* model. For example, not so long ago it was believed that albumin was synthesized at a maximum rate under normal *in vivo* conditions. This concept was arrived at because hyperalbuminemia was not observed except in acute dehydration. To test this concept, studies were done *in vivo* to try to determine if the synthesis of serum albumin could be stimulated by a mechanism which was felt not to alter qualitatively the functions of the body. To this end, exogenous thyroid was administered and the fractional rate of disappearance of radioactive iodine labeled albumin increased along with an increase in the amount of iodide released from degraded albumin which appeared in the urine. Thus, at least the metabolic turnover of albumin could be stimulated [25].

This study applied only to the fractional rate of protein synthesis—the absolute rate must take into account the total mass of protein synthesized or degraded. Marked changes in absolute turnover may be missed if only the fractional rate is measured. Other hormones are important in regulating the rate of protein synthesis within the liver. Cortisone, for example is not antianabolic in terms of albumin metabolism but actually stimulates albumin synthesis. Insulin appears to be required for optimal polysome aggregation. Data are available which indicate that the other hormones such as growth hormone actively stimulate hepatic protein synthesis. Probably an integrated hormonal "milieu" is the best setting for normal protein synthesis. The mechanism by which these hormones act is certainly not clearly understood, though it is probable that a stimulation of RNA metabolism including certain steps in translation are involved [9, 10, 12, 13, 25, 26, 28, 36]. Hormones are not the only agents to effect albumin synthesis but nutrition, stress, environment as well as disease and genetics also play vital roles [7, 20, 28, 38].

Not only can there be active stimulation of protein synthesis in the absence of disease states but protein synthesis can be inhibited under *in vivo* conditions. Using albumin again as an example, it has been clearly shown that the recip-

[1]Supported by the Medical Research Service of the Veterans Administration; National Institutes of Health Grants AA 00959 and HL 09562 and the Louise and Bernard Palitz Fund.

Copyright © 1980 ANKHO International Inc.—0091-3057/80/130031-06$01.10/0

TABLE 1

FACTORS INFLUENCING PROTEIN METABOLISM

1. Protein Concentration, Pool Size and Distribution
2. Hormonal Balance
3. Nutritional Status
4. Environment
5. State of Health

rocal changes so often seen in patients with liver disease [12], namely a depressed albumin level in association with an elevated globulin level, are clearly the end result of a mechanism attempting to regulate colloid content. This has been demonstrated *in vivo* and *in vitro*, using exogenous colloids such as gamma globulin or dextran as well as in animals that have been hyperimmunized and are undergoing rapid increment in their globulin levels [13]. Under these circumstances the serum albumin level fell, albumin pool size decreased and albumin synthesis decreased even further than did albumin degradation. However, when the added colloid was albumin, then the further accumulation of albumin was prevented by an increase in degradation without a decrease in synthesis [22].

I mention these particular studies to point out that the measurement of albumin metabolism or any serum protein metabolism *in vivo* is a highly complex matter. There are many factors interrelating to and influencing (Table 1) protein distribution, synthesis, and degradation. There are so many *in vivo* responses which can take place following stress that it is difficult to predict any end result even though a specific experimental design has been planned.

Thus one must use very specific models but at present every model system can be effectively criticized and extrapolation of data obtained from one system to another must be done with caution.

### *Cirrhosis—Albumin Synthesis*

In patients with cirrhosis of the liver, secondary to chronic ethanol consumption, serum albumin levels are observed to be depressed [24]. However, this depression, while frequently associated with an elevation in the gamma globulin level, is not always associated with a decreased total exchangeable albumin pool [27]. Of course these patients had ascites and the total exchangeable albumin pool, which consists in these patients of an additional pool within the ascitic fluid, was significantly elevated. These studies suggested that the serum albumin level was not necessarily a good index of either the exchangeable albumin pool or perhaps of albumin synthesis or both. Studies were then performed on patients with ascites utilizing techniques which could measure albumin synthesis over a short period of time and it was shown that albumin synthesis was not necessarily reduced in these subjects, even though they were quite ill. Of course these data did not indicate what was happening to these subjects prior to their hospitalization while they had still been consuming large quantities of ethanol. Models therefore had to be chosen which could not only separate 2 factors (nutrition and ethanol toxicity) but could dissect some of the intracellular processes which influence synthesis and secretion [27].

### *Albumin Synthesis*

Ethanol exposure has no single action for it impedes rapidly the apparent synthesis of some but not all serum proteins [14–17, 29]. I will primarily discuss serum albumin, not because albumin necessarily is so vital, but because it is a protein synthesized on hepatic polysomes bound to the endoplasmic reticulum. It is secreted through the Golgi apparatus but is not modified within the Golgi because there are no carbohydrate moities to be attached. Further, it is not a protein that is subject to degradation following performance of one specific function. The albumin synthetic process however is most complicated. There are both bound and free polysomes and the bound polysome appears responsible for the synthesis of secreted proteins. It appears that in terms of albumin, the free polysome is responsible for the initial synthesis of a pre-proalbumin molecule which contains a signal peptide which binds to the endoplasmic reticulum. This signal peptide is apparently hydrolyzed from the final albumin molecule so that the completed molecule appears within the plasma in the absence of this signal peptide [5]. If this proteolysis is interfered with, then secretion stops and synthesis stops or at least is inhibited [1,8]. Thus the secretion of albumin from the cell plays a significant feedback role in the regulation of synthesis. Furthermore the mRNA for albumin is rather long lived and stable [39] and appears to be held in a ribonucleoprotein particle within the cytosol [34,37] such that it is available to the free polysome for initiation of synthesis of the signal peptide complex and to restart albumin synthesis once the acute emergency caused by starvation or toxicity has passed. Other mRNA's that are short lived would have to be resynthesized and while this would not take a long period of time, the albumin mRNA is always ready to start its protein synthetic process. There are numerous peptide forming steps in the protein synthetic process where regulation or interference can occur including initiation, and the subsequent translational steps in addition to the availability of the various tRNA amino acid esters as well as signal peptide proteolysis and finally secretion.

### *Ethanol and Albumin Synthesis and Secretion*

Utilizing the isolated perfused rabbit liver and determining the amount of radioactive albumin secreted into the perfusate, it was shown that the administration of ethanol interfered with the apparent synthesis of serum albumin. This decrease appeared to be more permanent if the livers were derived from fasted donors; for under these circumstances, the administration of excess amino acids in the perfusate, a procedure which has been able to reverse the depression of the synthesis of albumin in the presence of ethanol in livers from fed donors was no longer effective. Further perfusion of livers from fasted donors, resulted in a disaggregation of both the bound and free polysomes, whereas, when the liver of well fed donors was tasted, ethanol added to the perfusate resulted in a disaggregation of only the endoplasmic membrane bound polysome. During the acute exposure to ethanol, over a period of a few hours, a loss of RNA did not occur (Table 2).

Using livers from fed donors and inhibiting EtOH metabolism by adding 1.5 mM 4-methyl pyrazole (4-MP) to the perfusate, polysome disaggregation was prevented but albumin and urea synthesis remained low. The lactate/pyruvate ratios were minimally altered from control values indicating the effectiveness of the 4-MP. When livers from fasted

TABLE 2
ALBUMIN SYNTHESIS

| | Fed Donors | | Fasted Donors | |
|---|---|---|---|---|
| | Albumin Synthesis | Bound Polysome Aggregation | Albumin Synthesis | Bound Polysome Aggregation |
| EtOH 200 mg% | ↓ | ↓ | ↓ | ↓ |
| EtOH 200 mg% + 4MP 1.5 mM | ↓ | C | ↓ | C |
| Acetaldehyde 2 mg% | ↓ | C | C | C |
| Acetaldehyde 2 mg% + 4MP 1.5 mM + Disulfiram 0.3mg% | C | C | ↑ | C |

Utilizing the perfused rabbit liver it was shown that ethanol (EtOH) added to the perfusate inhibited apparent albumin synthesis. The degree of polysome disaggregation was related to EtOH metabolism. Acetaldehyde inhibited albumin synthesis only in the livers from fed donors and did not cause polysome disaggregation. Inhibition of acetaldehyde metabolism returned albumin synthesis to control levels.
4MP=4-methyl pyrazole.
C=Control.

donors were employed and ethanol metabolism was inhibited with 4-MP, albumin synthesis remained at low levels but was not different from that seen during fasting per se; urea synthesis and polysome aggregation were also maintained at the fasting rate. Thus ethanol metabolism seems to be responsible for polysome disaggregation in the "fed" and "fasted" livers but albumin and urea synthesis vary according to the absolute nutritional state of the liver [21, 23, 27, 28, 29].

Acetaldehyde (2 mg/100 ml of perfusate) inhibits albumin and urea synthesis in the "fed" liver without polysome disaggregation but acetaldehyde has no effect in livers from fasted donors. Further, the inhibition of acetaldehyde metabolism with 4-MP and disulfiram (0.3 mg/100 ml) improved albumin synthesis in livers from fed donors, and actually resulted in a stimulus to albumin synthesis in livers from fasted donors [32]. The chelating agent, penicillamine also stimulated albumin synthesis is the fasted livers but the mechanism of action of these agents is not known. Thus, ethanol, ethanol metabolism, and acetaldehyde have differing effects on protein synthesis and these effects are governed by either feeding or fasting. These observations indicate the high degree of complexity of the effects of ethanol consumption on a single protein's production even when using a specific and controlled model system.

These are acute studies, that is, the livers are removed from animals who up until the fasting or the day of the experiment had been fed ad lib, and therefore more chronic studies were undertaken. Rabbits were given 1–4 g of ethanol/kg of body weight by stomach tube for 3 weeks prior to surgery [31]. Studies were then undertaken to determine if these rabbits would be less or more sensitive to the acute effects of ethanol. When ethanol was added to the perfusate, albumin synthesis in the obtained livers decreased to an equivalent degree as that seen when the donors had been maintained on a regular diet. Livers from animals essentially fasted, that is, not given alcohol the day prior to the study, nor any additional food, likewise behaved as did livers from normal fasted control animals. There were no significant alterations in the degree of depression of the lactate/pyruvate levels, and urea synthesis was equivalently depressed. Therefore, by feeding ethanol to these rabbits by stomach tube, we were unable to determine any significant protection against the acute effects of ethanol in the rate of apparent synthesis of serum albumin, urea synthesis or lactate/pyruvate levels (Table 3).

It was not possible to separate synthesis from secretion in these studies. The $^{14}C$ carbonate even when used as a pulse label, persists for some time and radioactive albumin continues to be released into the perfusate from the liver for as long as 80–100 minutes. This could in part be due to continued incorporation of the label, though only approximately 10% of the label is available following 10–15 minutes. In addition it is possible that there are many pathways within the cell by which the newly synthesized protein can reach the external milieu. While these pathways are only speculative at present, it is true that circuitous vascular pathways are known for many organ systems.

Decreased intracellular transport of proteins has been reported following chronic exposure to ethanol with accumulation of intracellular hepatic protein [2, 3, 35]. We turned to the isolated rat hepatocyte to attempt to study protein release in the absence of alterations of protein synthesis. Hepatocytes were isolated by standard techniques although there are probably as many standard techniques as there are investigators. We have utilized livers from fed or fasted donor rats which were cannulated through the portal vein and maintained with a high blood flow and subjected to a collagenase solution in the absence of calcium. Hepatocytes were incubated not in a Krebs Henslite buffered solution but in a Henks buffer, which does not contain carbonate buffer. These cells were then pulsed for 2.5 to 7 minutes with $^{3}H$ valine. The cells were then washed free of the $^{3}H$ valine, resuspended in the incubation media which now contained the substance to be tested. Included in this media, was 15 mM valine which would interfere significantly with any incorporation of $^{3}H$ valine that happened to persist following

TABLE 3

CHRONIC ETHANOL STUDIES

| Donor | Diet | Liver Wt g | Perfusate | Fed Donors Albumin Synthesis (mg/100g/hr) | Fed Donors Urea Synthesis (mg/100g/hr) | Bound Polysome Aggregation | Donor Blood EtOH Hours after Dose 1/2 to 1 mg% | Donor Blood EtOH Hours after Dose 5 to 5-1/2 mg% |
|---|---|---|---|---|---|---|---|---|
| 1 | Control | 50 ± 5 | Control | 21 ± 1 | 37 ± 4 | 61 ± 2 | — | — |
| 2 | EtOH | 43 ± 3 | 200 mg% EtOH | 10 ± 2 | 20 ± 1 | 47 ± 2 | 168–273 | 103–175 |
| 3 | Control | 41 ± 2 | 200 mg% EtOH | 11 ± 1 | 20 ± 4 | 39 ± 7 | — | — |
| 4 | EtOH | 48 ± 3 | Control | 21 ± 3 | 30 ± 2 | 56 ± 4 | 156–320 | 133–230 |

the washes or was released free from internal cellular protein degradation. A short period of labeling had to be chosen, such that synthesis would not be tampered with and secretion would be just beginning when the test substance was added, otherwise we would not be able to tell whether we were again interfering with synthesis or secretion. Information such as this has also been obtained by other investigators [17,19]. Other studies were performed in which the hepatocytes were kept in contact with the $^{3}H$ valine at a constant specific activity (through the addition of significant quantities of unlabeled valine) and samples of these cells were obtained at various times over a course of 2–2.5 hours. Cells that had also been exposed to ethanol during this incubation period were compared to control cells [18]. Therefore, under these circumstances we would be able to measure synthesis plus secretion and secretion per se in the absence of any interfering or potentially interfering substance while the labeling of protein was taking place in the former study. In the synthesis studies, a decrease in incorporation of $^{3}H$ valine into total medium protein was seen [18]. In the secretion studies whether the livers were from fed or fasted donors, there was no difference in the rate of release of prelabeled protein when the liver cells were incubated in ethanol compared to control incubation and thus acute ethanol studies did not in this system appear to influence the rate of secretion per se. In the synthesis studies a significant decrease in incorporation of $^{3}H$ valine into medium proteins was noted when ethanol was present in the medium [18]. Lactate levels were increased in the cells exposed to ethanol and rates of urea synthesis were depressed (Tables 4 & 5) but we do not have any absolute measurement of how well these cells were metabolizing ethanol or at what metabolic rate these cells were operating. Studies have not been conducted with acetaldehyde nor with 4-methyl pyrazole nor with other substances which alter the redox state as does ethanol but all of these are contemplated for the future. It is at present clear that acute addition of ethanol had not effect on the rate of secretion of prelabeled protein, that is, protein that was labeled in the absence of ethanol. Certainly, the microtubules, as has been shown by Dr. Lieber and his coworkers, are significantly altered [4]. The liver increases in size and there is an increase in protein content but the acute effects of ethanol on protein secretion do not appear to be specific and probably result in a significant feedback inhibition of protein synthesis within the liver cell in an attempt to prevent the accumulation of protein within the cell which would then be considered foreign since it would be normally destined for export. This may well play an important role in the normal failure of the cell to accumulate within its cytosol protein destined for export. Cells obtained from animals

TABLE 4

PROTEIN SECRETION

| Donor | Pulse Time (min) | EtOH | Minutes after Label 30 | 60 | 90 | 120 |
|---|---|---|---|---|---|---|
| | | | % of Cell Batch Control | | | |
| Fasted | 2.5 | 50–100 mM | 102 ± 6 | 113 ± 10 | 98 ± 6 | 100 ± 7 |
| Fed | 2.5 | 50–100 mM | 94 ± 6 | 99 ± 2 | 100 ± 3 | 103 ± 3 |
| Fed Fasted | 7.5 | 100 mM | 94 ± 4 | 98 ± 4 | 98 ± 3 | 106 ± 4 |

Number of Studies: 10 studies were done in the fed and fasted tissue using the 2.5 minute pulse time and 6 studies used the 7.5 minute pulse time. See [18].

TABLE 5

LACTIC ACID AND UREA SYNTHESIS

| Donor | No. of Studies | Δ Lactate Levels ($\mu$M/10$^6$ Cells) | Urea Synthesis ($\mu$M/10$^6$ Cells/Hr) | |
|---|---|---|---|---|
| | | | Control | EtOH |
| Fed EtOH 50–100 mM | 10 | 0.34 ± 0.11* | 22 ± 1.8 | 12.7 ± 0.9* |
| Fasted EtOH 50–100 mM | 12 | 0.40 ± 0.14* | 16 ± 2.3 | 10.1 ± 1.3† |

Lactate levels were determined at 15′, 60′ and 120′ in control and experimental studies. The Δ was calculated for the differences between the 15′ and 120′ lactate levels in the media in the ethanol (EtOH) treated cells minus any change in the lactate levels in the media from cells incubated without EtOH.

Values are the mean ± SEM.

*Indicates $p$ value less than 0.01.

†Indicates $p$ value less than 0.05.

See [18].

placed on an alcohol diet for 4 to 8 weeks likewise do not show any prediliction to a specific deficit in secretion measured by our particular technique.

Finally, we do not know why ethanol ingestion or metabolism interferes with protein synthesis. We do not know if an intermediate metabolic step is involved. There is evidence that acetaldehyde interferes with protein metabolism and protein synthesis both in the heart [33] and in the liver but it does so without causing polysome disaggregation.

In terms of ethanol's effects on protein synthesis it appears that the polyamines play important roles. The polyamines have been shown to affect cellular regeneration, RNA metabolism and protein synthesis [11]. The addition of ornithine, a precursor, for polyamine synthesis, to the perfusate along with ethanol, prevented polysome disaggregation and thus we studied the polyamine, spermine, to determine if spermine could prevent some of the ethanol induced effects. Spermine can result in polysome reaggregation both of the bound and of the free in the presence not only of alcohol, but also of carbon tetrachloride [30] and this suggests that the polyamines and the alcohols are not necessarily working totally at the endoplasmic reticulum level since the free polysome is not attached to the endoplasmic reticulum. Perhaps one of the reactions sensitive to ethanol may occur during an early stage of initiation. Of course more than one step could clearly be affected and these preliminary studies are suggestive of the complex nature of protein synthesis, even in isolated systems, and the interaction of these systems with the metabolism of ethanol. Further studies are obviously necessary and will provide us with work for a long time to come.

## REFERENCES


1. Algranati, I. D. and D. D. Sabatini. Effect of protease inhibitors on albumin secretion in hepatoma cells. *Biochem. biophys. Res. Commun.* **90:** 220–226, 1979.
2. Baraona, E., M. A. Leo, S. A. Borowsky, *et al.* Alcoholic hepatomegaly: Accumulation of protein in the liver. *Science* **190:** 794–795, 1975.
3. Baraona, E., M. A. Leo, S. S. Borowsky, *et al.* Pathogenesis of alcohol-induced accumulation of protein in the liver. *J. clin. Invest.* **60:** 546–554, 1977.
4. Baraona, E., Y. Matsuda, P. Pikkarainen, S. Finkelman and C. S. Lieber. Exaggeration of the ethanol-induced decrease in liver microtubules after chronic alcohol consumption: Role of acetaldehyde. *Gastroenterology* **76:** 1274, 1979.
5. Blobel, G. and B. Dobberstein. Transfer of proteins across membranes. *J. cell. Biol.* **67:** 835–851, 1975.
6. Bjørneboe, M. Studies on the serum proteins in hepatitis. I. The relation between serum albumin and serum globulin. *Acta. med. scand.* **123:** 393–401, 1946.
7. Buehler, B. A. Hereditary disorders of albumin synthesis. *Ann. Clin. Lab. Sci.* **8:** 283–286, 1978.
8. Dorling, P. R., P. S. Quinn and J. D. Judah. Evidence for the coupling of biosynthesis and secretion of serum albumin in the rat. *Biochem. J.* **152:** 341–348, 1975.
9. Enwonwu, C. O. and H. N. Munro. Changes in liver polyribosome patterns following administration of hydrocortisone and actinomycin D. *Biochim. biophys. Acta* **238:** 264–276, 1971.
10. Feldhoff, R. C., J. M. Taylor and L. S. Jefferson. Synthesis and secretion of rat albumin in vivo, in perfused liver, and in isolated hepatocytes. *J. biol. Chem.* **252:** 3611–3616, 1977.
11. Janne, J., H. Pössö and A. Raina. Polyamines in rapid growth and cancer. *Biochim. biophys. Acta.* **473:** 241–293, 1978.
12. Jefferson, L. S. and A. Korner. A direct effect of growth hormone on the incorporation of precursors into proteins and nucleic acids of perfused rat liver. *Biochem. J.* **104:** 826–832, 1967.
13. Keller, G. H. and J. M. Taylor. Effect of hypophysectomy and growth hormone treatment on albumin mRNA levels in the rat liver. *J. biol. Chem.* **254:** 276–278, 1979.
14. Khursheed, N., J. Jeejeebhoy, H. O. Joseph, R. Gordon, M. Greenberg, M. J. Phillips, A. Bruce-Robertson and U. Sodtke. Albumin, fibrinogen and transferrin synthesis in isolated rat hepatocyte suspensions. *J. Biochem.* **146:** 141–155, 1975.
15. Morland, J. Incorporation of labelled amino acids into liver protein after acute ethanol administration. *Biochem. Pharmac.* **24:** 439–442, 1974.
16. Morland, J., T. Hoom and H. Prydz. The influence of ethanol feeding on the activities of factors II, VII, IX, and X in rats. *Thromb. Haemostasis* **36:** 532–536, 1976.
17. Morland, J. and A. Bessesen. Inhibition of protein synthesis by ethanol in isolated rat liver parenchymal cells. *Biochim. biophys. Acta.* **474:** 312–320, 1977.

18. Morland, J., M. A. Rothschild, M. Oratz, J. Mongelli, D. Donor and S. S. Schreiber. The lack of effect of ethanol on protein export in isolated rat hepatocytes. *Gastroenterology* **80:** 159–165, 1981.
19. Morland, J., A. Bessesen and L. Svendsen. Incorporation of labelled amino acids into proteins of isolated parenchymal and nonparenchymal rat liver cells in the absence and presence of ethanol. *Biochim. biophys. Acta.* **561:** 464–474, 1979.
20. Munro, H. N. Free amino acid pools and their role in regulation. In: *Mammalian Protein Metabolism, Vol. 4,* edited by H. N. Munro. New York: Academic Press, 1970, pp. 299–386.
21. Oratz, M., M. A. Rothschild and S. S. Schreiber. Alcohol, amino acids, and albumin synthesis. II. Alcohol inhibition of albumin synthesis reversed by arginine and spermine. *Gastroenterology* **71:** 123–127, 1976.
22. Oratz, M., M. A. Rothschild and S. S. Schreiber. Albumin-osmotic function. In: *Albumin Structure, Function and Uses,* edited by V. M. Rosenoer, M. Oratz and M. A. Rothschild. New York: Pergamon Press, 1977, pp. 275–282.
23. Oratz, M., M. A. Rothschild and S. S. Schreiber. Alcohol, amino acids and albumin synthesis. III. Effects of ethanol, acetaldehyde, and 4-methylpyrazole. *Gastroenterology* **74:** 672–676, 1978.
24. Post, J. and A. J. Parek, Jr. Serum proteins in cirrhosis of the liver. *Archs intern. Med.* **69:** 67–82, 83–89, 1942.
25. Rothschild, M. A., A. Bauman, R. S. Yalow, *et al.* The effect of large doses of desiccated thyroid on the distribution and metabolism of albumin-$I^{131}$ in euthyroid subjects. *J. clin. Invest.* **36:** 422–428, 1957.
26. Rothschild, M. A., S. S. Schreiber, M. Oratz, *et al.* The effects of adrenocortical hormones on albumin metabolism studied with albumin-$I^{131}$. *J. clin. Invest.* **37:** 1229–1235, 1958.
27. Rothschild, M. A., M. Oratz and D. Zimmon, *et al.* Albumin synthesis in cirrhotic subjects with ascites studied with carbonate-$^{14}C$. *J. clin. Invest.* **48:** 344–350, 1969.
28. Rothschild, M. A., M. Oratz and S. S. Schreiber. Albumin synthesis. *New Engl. J. Med.* **286:** 748–757, 816–821, 1972.
29. Rothschild, M. A., M. Oratz and S. S. Schreiber. Alcohol, amino acids and albumin synthesis. *Gastroenterology* **67:** 1200–1213, 1974.
30. Rothschild, M. A., M. Oratz, S. S. Schreiber and B. Lane. $CCl_4$ induced hepatic polysome disaggregation with inhibition of protein synthesis reversed with spermine in rabbits. *Gastroenterology* **79:** 1165–1173, 1980.
31. Rothschild, M. A., M. Oratz and S. S. Schreiber. Albumin synthesis studied in livers from rabbits chronically exposed to EtOH. *Gastroenterology* **77:** A35, 1979.
32. Rothschild, M. A., M. Oratz, S. S. Schreiber and J. Mongelli. The effect of acetaldehyde and disulfiram on albumin synthesis in the isolated perfused rabbit liver. *Alcoholism: Clin. exp. Res.* **4:** 30–33, 1980.
33. Schreiber, S. S., K. Briden, M. Oratz and M. A. Rothschild. Ethanol, acetaldehyde and myocardial protein synthesis. *J. clin. Invest.* **51:** 2820–2826, 1972.
34. Shafritz, A., S. H. Yap and R. K. Strair. Regulation of albumin synthesis in rat liver. *Molec. Biol. Rep.* **5:** 1–2, 71–78, 1979.
35. Sorrell, M. F. and D. J. Tuma. Selective impairment of glycoprotein metabolism by ethanol and acetaldehyde in rat liver slices. *Gastroenterology* **75:** 200–205, 1978.
36. Sterling, K. The effect of Cushing's syndrome upon serum albumin metabolism. *J. clin. Invest.* **39:** 1900–1908, 1960.
37. Yap, S. H., R. K. Strair and D. A. Shafritz. Identification of albumin mRNPs in the cytosol of fasting rat liver and influence of tryptophan or a mixture of amino acids. *Biochem. biophys. Res. Commun.* **83:** 427–433, 1978.
38. Yap, S. H., R. K. Strair and D. A. Shafritz. Effect of a short term fast on the distribution of cytoplasmic albumin messenger ribonucleic acid in rat liver. *J. biol. Chem.* **253:** 4944–4950, 1978.
39. Wilson, S. H., H. Z. Hill and M. B. Hoagland. Physiology of rat-liver polysomes: Protein synthesis by stable polysomes. *Biochem. J.* **103:** 567–572, 1967.