Arh. hig. rada, *19* (supl. 1) (1968) 71.

INDUSTRIAL HYGIENE AND PATHOPHYSIOLOGICAL ASPECTS OF HEAVY METAL POISONINGS

ANA MARKIĆEVIĆ, KATA VOLODER, DANICA PRPIĆ-MAJIĆ

The results of studies on several aspects of poisoning caused by lead, mercury, mangenese, hard metal, nickel, and uranium are reviewed.

Studies on lead comprise the development of methods for the determination of lead in biological material, the analysis of pathophysiological processes and clinical manifestations of saturnism, and the elaboration of criteria for the assessment of working capacity in intoxicated workers.

Investigations concerning mercury poisoning include the determination of methods for the determination of mercury in biological material, observations on the pathophysiological and clinical manifestations of mercurialism, and the drawing up of criteria for the assessment of fitness for work in intoxicated workers.

In connection with the occurrence of manganism in the production of manganese alloys in Šibenik, studies were conducted on the clinical picture of manganism, technological processes in which the workers were exposed to manganese smoke and dust, and the measures to be undertaken to prevent manganism.

Results are presented of the follow up of a group of workers exposed to hard metal dust and the pathogenesis of pneumoconiosis caused by hard metal.

Work is reviewed on nickel allergy observed in galvanizers in various industrial establishments.

The review also includes results of observations on the harmful effect of uranium; in this connection polarographic methods have been developed for the determination of small amounts of this metal in the blood, urine, and kidneys.

Poisonings due to lead, mercury, and manganese, owing to the development of Yugoslav industry, have arisen as a serious occupational health problem. For this reason the Institute's research activities have to a considerable extent been connected with these problems. In the last years studies have also been conducted relating to the deleterious effect of hard metal and nickel, and methods have also been developed for the determination of uranium in biological material.

LEAD

Lead poisoning is one of the most frequent and most important occupational diseases in Yugoslavia (1). Thus, a large number of the Institute's studies have dealt with various aspects of the prevention and control of saturnism.

Lead determinations have been carried out in the atmosphere, biological material, pottery, and foodstuffs. They have been coupled with pathophysiological and clinical examinations in cases of poisoning.

Analysis of lead in biological material

For the determination of lead in biological material the spectrophotometric, dithizone, and polarographic methods have been used most often.

The *Oesterberg-Sjöholm* dithizone method (2) was not found precise enough for the analysis of iron-containing biological material. Moreover, this method, like the majority of other dithizone methods, requires washing of lead dithizonate by ammonium or potassium cyanide for removing dithizone in excess. As the dithizone in excess produces a »mixed« colour of the extract, these washings are often a source of considerable errors. We have therefore modified the *Oesterberg-Sjöholm* method by completely removing iron by means of cupferrone in a certain phase of the analytical procedure (following the mineralization of the sample but preceding lead extraction by dithizone), while lead extraction was performed at a relatively high pH (10.5). In this way the concentration of free dithizone was considerably reduced, which made the above mentioned washings unnecessary. Evidence was obtained that the »mono-colour« method modified in this way was reliable, sensitive, and precise. When the blood is analysed by this method, the standard error of individual measurements (made at the Beckman spectrophotometer at the wave length of 520 mμ) never exceeds ∓ 7 μg for the lead concentration of 25 to 500 μ/100 ml of blood. When there is a parallel analysis of two samples of the same blood, the standard error is reduced to $\mp 5\mu g$ (3).

A special study related to lead dithizonate. It was proved that one mol of lead is bound to two mols of dithizone. In this connection the concentration of dithizone and lead dithizonate in the state of equilibrium was determined. The relationship was also assessed between the extracted amount of lead and the concentration of hydrogen ions in the 5–11 pH range in the presence of citrates and cyanides. The Pb–dithizonate extraction constant amounts to 1.4×10^{-3} in the presence of citrates and 2.9×10^{-6} in the presence of cyanides (4).

A new basic electrolyte was introduced for the polarographic determination of small amounts of lead. It consists of 0.5 M succinic acid and 0.0081% gelatine. It has been proved statistically that under these polarographic conditions a precise determination of lead is possible in the solution of 10^{-6} mol Pb/l, i. e. 1 μg/ml (5).

By the modified dithizone method we determined the upper lead concentration limit in the blood of 195 subjects (100 males and 95 females) without any known lead exposure. The value of 60 μg/100 ml was taken as the upper normal value limit, which is the upper 90% tolerance limit with the condifence coefficient of 0.95 (6).

The modified dithizone method was also used for the analysis of lead in the blood and urine of outpatient and hospitalized patients of the Department of Occupational Diseases. It has been shown that the concentration of lead in the blood and urine is of no essential diagnostic significance.

The dithizone method has also proved useful for the measurement of lead in the cerebrospinal fluid, bonemarrow, and organs. According to the results obtained, the cerebrospinal fluid of non-exposed persons may contain up to 18 μg lead/100 ml. In persons exposed to dust and vapour of lead oxides, lead tetraethyl vapour, and in cases of peroral introduction of organic lead salts (lead tartarate, acetate, etc) from lead-glazed pottery into the organism, there may occur an increased concentration of lead in the cerebrospinal fluid. However, no statistically significant correlation was found between lead in the cerebrospinal fluid and the concentration of lead in the blood. The concentration of lead in the cerebrospinal fluid does not correspond to the clinical picture of poisoning (7).

The concentration of lead in the bone-marrow was analysed in a total of 56 patients; 48 of them were hospitalized owing to an increased lead absorption or manifest lead poisoning. The lead concentration in the bone marrow of controls did not exceed 25 μg/100 ml, while in the exposed group considerably higher concentrations, relating to the degree of poisoning, were most frequently observed; the highest value was 252 μg/100 ml. These studies have shown from one more aspect that the presence of lead is responsible for pathogenetic changes in the bone-marrow.

Examining the lead content in organs (the liver, spleen, and kidney) it has been found that in persons exposed to no lead either occupationally or in daily life the liver may contain 12–510 μg, the spleen 46–520 μg, and the kidney 46–405 μg of lead per 100 g of the fresh organ. It was tried to find an explanation of these great variations in different nutritional and living habits. In only one case the organs of a man who in his life had had repeated lead poisoning were analysed: his liver contained 1220 μg, the spleen 482 μg, and the kidney 705 μg lead per 100 g of the fresh organ (8).

Determination of coproporphyrin in urine

As the appearance of coproporphyrins in the urine is a reliable early sign of the pathologic effect of lead, special attention has been paid to the analysis of these compounds, and the fluorimetric determination of coproporphyrins in particular. Details are presented in a separate review (9). For the determination of normal values a group of 150 healthy persons (75 males and 75 females) without any known exposure to lead were

employed. The mean coproporphyrin value for males proved to be 154 μg/24 hours and for females 140 μg/24 hours, while the upper normal value for men was assessed as 241 μg/24 hours and for females 280 μg/24 hours. The difference of arithmetic means as regards sex was not statistically significant (10).

The determination of normal values allowed the differentiation between non-exposed and exposed persons. In the Department of Occupational Diseases 5140 urine samples taken from persons exposed to lead have so far been analysed. Almost in every case was the coproporphyrin finding a reliable indication of the increased lead absorption and the coproporphyrin concentration in most patients proved to be correlated with the intensity of poisoning. In this way the diagnostic values of coproporphyrin measurements in exposure to lead has been confirmed.

The relationship between the concentration of lead in the blood and coproporphyrin in the urine was the object of a separate study (N = 154). It was found that the results of lead concentration in the blood and coproporphyrin values were normally distributed. Although the regression equation for the unknown concentration of coproporphyrin in the urine was calculated from the known concentration of lead in the blood and vice versa, it was proved that, owing to very wide confidence limits based on the coproporphyrin findings in the urine, not even an approximate concentration of lead in the blood and vice versa could be determined (11).

Determination of delta–amino–levulinic acid in the urine

Lead inhibits haem synthesis not only at the level of incorporation of iron into the porphyrin ring but also at the level of the formation of porphobilinogen, the porphyrin precursor. The results of this inhibition is the increased extraction of delta-amino-levulinic acid. In order to ascertain the diagnostic value of delta-amino-levulinic acid measurements, we have analysed a large number of urine samples of exposed and non-exposed persons. By using the method after *Mehani* (12), the normal concentrations of delta-amino-levulinic acid in persons without any known exposure to lead proved to be 1692 ± 507 μ/1000 ml urine or 1839 ± 632 μg/24–hour urine. Comparison with other laboratory findings has shown that this analysis is a very useful indicator in the diagnosis of lead poisoning, especially relating to short-lasting exposures.

Analysis of lead in pottery and foodstuffs

Lead-glazed pottery is still used in Yugoslavia and has often proved to be the cause of very severe lead poisonings. The intensity of lead extraction from lead-glazed pottery was examined in relation to temperature, pH, and the presence of various inorganic and organic acids (13). A whole series of compounds usually present in foodstuffs have proved to dissolve lead from the glaze in a considerable degree, especially at higher temperatures.

The foodstuff examined in more detail were flour and corn. In this connection lead was also determined in millstones, and a modification of the mineralization method used for the analysis of blood and other biological material has been evolved (14).

Pathophysiology and clinical aspects of saturnism

Clinical experience at home and abroad has shown that from the practical point of view it is important to know the pathophysiological effect of lead on only some of the organs and organic systems: the blood and blood-forming organs, the neuromuscular apparatus, the central nervous system, and the kidneys.

Intensive studies have been conducted at the Institute concerning morphologic changes in erythrocytes as the most prominent hematologic manifestation of lead poisoning (15–19). The work is reviewed in greater detail in a separate article (20).

Studies have also been conduced concerning the effect of lead ions on the hypotonic resistence of erythrocytes (21). The degree of erythrocyte osmotic fragility is often used as a diagnostic test and an index of red blood cell vitality. Lead produces a pronounced increase in the hypotonic resistence of rat erythrocytes, while the ions of some other metals – strontium, mercury, and uranium – produce no such changes.

In order to elucidate neuromuscular changes in the clinical picture of saturnism, the effect of lead on skeletal muscles and the peripheral nervous system was investigated.

Studying the effect of lead on the synaptic transmission (22, 23) it has been observed that lead ions in the concentration of 5–40 mM/l produce a partial and sometimes also a complete block of the synaptic transmission. As lead ions decrease the release of acetylcholine while at the same time ganglionic cells become even more sensitive to exogenous acetylcholine, it was suggested that lead mainly affects the preganglionic nerve endings. In these concentrations lead does not seem to affect nerve conduction. The investigations have also shown that calcium ions have an antagonistic effect and that the inhibition of the synaptic transmission produced by lead ions can be eliminated by adding calcium ions to the perfusion solution. The antagonizing action of calcium ions might be explained by assuming a competitive action of lead and calcium ions for the same protein molecules, lead forming stronger protein complexes than calcium. An excess of calcium ions might eliminate lead ions from their protein complexes and restore the normal activity of the enzyme-like factor responsible for the liberation of acetylcholine.

Investigating the effect of lead on muscles (23), lead ions proved to produce an increased sensitivity of the muscle to acetylcholine in lower concentrations and the Lundsgaard effect in higher concentrations. The effect of lead ions is reversible. It seems that the effect of lead on

muscles cannot be explained by changes in carbohydrate metabolism or prevention of phosphocreatine resynthesis but by some changes in the membrane of muscular fibres.

A very interesting problem of Yugoslavia is the effect of lead on the kidney, because in this country not only industrial but also agricultural workers (pottery) are often endangered by lead (13). Literature data on the problem of kidney lesions due to lead are controversial. While some authors ascribe pronounced nephrotoxic effects to lead (24–27), others deny it entirely (28,29). Owing to a comparatively large number of patients having been hospitalized at our Department after lead poisoning, we have been in a position to study the problem in great detail. The results obtained speak for the nephrotoxic effect of lead (30, 31). The changes observed were not always of the same kind, and for this reason we do not think it justified to speak about »nephropathia saturnina« as a clinical and pathoanatomical entity. In our opinion, kidney lesions caused by lead are mostly functional and transitory in character, but the possibility of lead also producing organic lesions in the conditions of long-lasting, heavy exposures should not be ruled out. Functional lesions are considered to be due to disorders in the intrarenal circulation, i. e. to the spastic effect of lead on blood vessels and the kidney and a direct or indirect effect of lead on tubules. Disorders of partial kidney function have, as a rule, been transitory.

In the study of the hepatotoxic effect of lead (32) in 87 patients (treated at the Department of Occupational Diseases) there have invariably been three signs speaking for a slight liver function disorder: a moderate to light hyperbilirubinemia, a slightly increased activity of serum glutamic pyruvic transaminase, and a pronounced increase of alpha-2-globulin values.

Transitory hypertonia (30) as a result of the spastic effect of lead on arterioral musculature has been observed in a very few cases, probably because it was not possible to observe the patients from the first day of poisoning.

The study of hypertension in workers exposed to lead in a lead battery plant has shown that no more frequent occurence of the increased blood pressure in lead exposure should be expected (33).

The most frequently encountered clinical type of lead poisoning in the patients observed was the gastrointestinal type (34).

Investigating the effect of the Na_2Ca EDTA complexon in lead poisoning and applying it in a very wide concentration range, from 2.4 to 24 g a day, it has been proved that Na_2Ca EDTA in all doses, from 2.4 to 24 g a day, has a very good effect on appeasing the symptoms of poisoning. Lower daily doses of 2.4 g have from the clinical point of view had a weaker effect (35). Yet, all doses of the complexon have had a positive effect on the release of lead and the normalization of laboratory findings. Comparing lead concentrations in the urine with lead concentration in the blood it was possible to confirm the observations of other authors (36) that only a small portion of the drug is used for the pro-

duction of chelates with lead. Practically no better effect is produced with the Na_2Ca EDTA doses larger than the usual ones (2.4 – 4.8 g a day). What is significant however, is that high doses (up to 24 g a day) produced no toxic effects either (37).

As to the frequency of drug application the results obtained are again in agreement with reports in literature (38), according to which in lead poisoning the most successful administration of the complexon Na_2Ca EDTA should last 2–3 days, with intervals of 5–7 days between each cure.

In view of our year-long experience in the study of the pathophysiology and clinical aspects of saturnism, we also thought it useful to work out criteria for the assessment of working ability in occupational lead poisoning (39). This has in no small measure facilitated the industrial physician's work on the evaluation of working ability in this most frequently encountered occupational intoxication in Yugoslavia.

MERCURY

The study of occupational mercury poisoning is of special importance to Yugoslavia. Mercury compounds are increasingly employed in various industrial processes, especially in the production of fungicides for agricultural use. Besides Yugoslavia has one of the largest European mercury mine – Idria.

Within research into the problems of mercurialism, the Institute has been concerned with the determination of mercury in biological material, the pathophysiological and clinical manifestations of poisoning, the possibility of the prevention of workers in exposed working places, and the elaboration of criteria for the assessment of the working ability of mercury-poisoned workers.

Laboratory analysis

A simple procedure has been evolved for the digestion of mercury-containing biological material and for the determination of mercury by the reversion method (40). The procedure is based on the complete evaporation of mercury in the course of the mineralization of biological material and the absorption in water solution of potassium permanganate and sulphuric acid. After that mercury ions are determined by dithizone using the reversion method. The standard error of this method does not exceed 8 μg Hg/100 ml of blood at the concentration of 350 μg Hg/100 ml or 1.6 μg Hg/100 of urine at the concentration of 68 μg Hg/100 ml of urine. The same method can also be applied for the determination of mercury in the cerebrospinal fluid and other tissues.

Methods have also been developed for the determination of mercury vapour and aerosols in the air (41, 42).

Pathophysiological and clinical investigations

Studying the effect of mercury ions on the synaptic transmission it has been found that mercury ions affect the synaptic transmission in the same concentrations as lead ions, only the effect is considerably slower. Unlike the effect of lead ions, the effect of mercury ions on the contraction of the nictitating membrane is irreversible. Mercury ions also decrease the release of acetylcholine but this effect is fully reversible, while the ganglionic cells remain insensitive to exogenous acetylcholine (43, 44). It has been assumed that mercury ions, unlike lead ions, mostly affect the postsynaptic element by decreasing the sensivity of ganglionic cells to acetylcholine.

Investigating the effect of mercury ions on prothrombin activity *in vitro* (45) it has been shown that addition of mercury ions to the human or rat blood in the concentration of 12.5 to 52.5 μg/ml considerably prolongs the clotting time. This effect depends on the length of exposure and the concentration of mercury ions. It is assumed that this is due to an interaction of mercury ions with the sulfhydril groups of plasmatic proteins. The difference between results obtained in rat and human blood is supposed to be due to the number of SH-groups responsible for coagulation in the rat and human blood.

The verification and assessment of hematologic analyses have been carried out in 189 miners and smelters in the Mercury Mine Idria and 70 workers from a felt hat factory exposed to mercury vapour (46). In relation to controls, no deviation from normal was observed not only in the blood count of exposed but also in the blood count of poisoned workers.

In collaboration with the Medical Faculty in Zagreb the occurence of the oral syndrome in subacute and exacerbated chronic mercurialism was investigated (47). On the basis of these studies recommendations were made for the therapy and prophylaxis of lesions in the oral cavity due to mercury.

In group of 140 workers exposed to organic mercury dust in the »Radonja« factory in Sisak the occurence of clinical symptoms and mercury elimination in the urine was observed (48). It was not possible to establish any correlation between clinical manifestations and the concentration of mercury in the urine.

The effect of mercury on the activity of some enzymatic systems has been examined as well. The results have shown that exposure to mercury increases the activity of alkaline phosphatase, glutamic-oxalacetic transaminase, and glutamic-pyruvic transaminase (49).

Criteria for the assessment of working ability in occupational mercurialism have been worked out (50).

In the mercury mine at Idria working conditions and workers'safety have been investigated. As a first step towards improving workers'protection the quantitative determination of mercury in the atmosphere of working environment and the assessment of thermal environmental factors have been completed (51). A proposal for the construction of respirators for protection against mercury vapour was made on the basis of the results of this study (52, 53).

MANGANESE

Manganese poisoning has also proved important for Yugoslav occupational pathology. Immediately before the Second World War even the general public took interest in manganism when in the Šibenik factory »La Dalmatienne« (in 1939) a larger group of workers suddenly fell ill with some obscure neurological and mental symptoms. Two diametrically opposed opinions arose as to the cause of the disease: one ascribing it to occupational manganese exposure and one categorically denying it (54, 55, 56).

In the course of the subsequent 4 years workers exposed to manganese were studied in great detail. The clinical picture of manganism was analysed, as well as the technological process in the production of manganese alloys where workers were exposed to manganese smoke and dust. The recommendations given for the prevention of occupational manganism were based on these studies (57, 58).

With regard to scarce literature data on the acute effect of manganese, we have investigated at the Institute the effect of bivalent manganese ions on the synaptic transmission (59). It has been observed that the perfusion of ganglia by the Locke solution containing more than 10 μg of bivalent manganese ions prevents the contraction of the nictitating membrane to preganglionic nerve stimulation. In this case, too, calcium ions have an antagonistic effect, preventing the block of ganglionic transmission in the same way as they do in the case of lead and magnesium ions. Thus, the effect of manganese is qualitatively equal to the effect of lead. However lead acts in concentrations 100 times smaller than those necessary for manganese to produce the same effect.

HARD METAL

In the last years we have had a chance of following up a group of workers exposed to hard metal dust (sinter metal) (60, 61). In three of the exposed workers pneumoconiosis due to hard metal was detected.

Hard metal is a mixture of highly soluble carbides, tungsten, titanium, and tantalum, which give it hardness, and cobalt which bonds carbides.

The question of the pathogenesis of pneumoconiosis caused by hard metal is still open. Most authors think that there is an allergic sensibilisation (62–64) and that cobalt might be the bearer of antigenic properties (65).

Examining the group of exposed workers and following up the diseased in the course of 2–4 years, no evidence has been obtained that a sensibilization to cobalt is at the bottom of the occurrence of pneumoconiosis due to hard metal (66). The group of exposed workers is being folowed up.

NICKEL

Among pathogenic properties of nickel, the production of nickel allergy is the most frequent and best known. Of special interest to occupational medicine is the relationship between non-occupational and occupational allergoses due to nickel, because in everyday life there is an almost permanent contact with some nickel plated objects or objects made of nickel alloys (67).

We reported on the first case of nickel allergy in 1960 (68). Later the occurrence of nickel eczema was analysed in galvanizers in five galvanization departments of three Zagreb plants (»Rade Končar«, »Ghetaldus«, and »Ikom«). In addition, cross sensibilization was studied in exposed workers in the already quoted factories, as well as in the enamel ware production »Gorica«, cement production »Sloboda« in Podsused, and the factory »Metal« in Remetinec (69).

URANIUM

Within studies of the effect of some metal ions on prothrombin activity *in vitro* the effect of uranyl ions was studied as well. It has been found that uranyl ions produce no changes in the prothrombin index (45).

The effect of chelatogenic substances on the retention of uranium in the kidney has been investigated with a view to obtaining more data on the action of some chelating agents on uranium retention in the kidney. The use of diethylene triamine penta-acetic acid (DTPA) has proved to produce a considerable decrease in the amount of uranium in the kidneys (70).

Polarographic methods have been developed for the determination of small amounts of uranium in the blood (71, 72, 73), urine and kidneys (74).

References

1. *Markićević, Ana, Beritić, T.:* Profesionalne bolesti i intoksikacije liječene u Odjelu za profesionalne bolesti od 1953. do 1962. god., Arh. hig. rada, *14* (1963), 299.
2. *Vesterberg, R., Sjöholm, O.:* Microdetermination of Lead in Biological Material, Mikrochem. ver. Mikrochim. Acta, *38* (1951) 81.
3. *Weber, O. A., Voloder, Kata, Vouk, V. B.:* Prilog određivanju malih količina olova u krvi, Arh. hig. rada, *3* (1952) 296.
4. *Weber, O. A.:* Fizičko-kemijska svojstva ditizonata nekih metala i primjena na određivanje u biološkom materijalu, Disertacija, Zagreb, 1956.
5. *Weber, O. A.:* Note on Polarographic Determination of Small Amounts of Lead, Croat. Chem. Acta, *29* (1957) 73.
6. *Vouk, V. B., Voloder, Kata, Weber, O. A., Purec, Ljerka:* Normal Values of Lead Concentration in Human Blood, Arh. hig. rada, *6* (1955) 277.
7. *Prpić-Majić, Danica, Beritić T.:* Olovo u likvoru kod kliničnog saturnizma, Arh. hig. rada, *18* (1967) 347.
8. *Đurić, D., Šarić, M., Malek, Đurđa:* Vrijednosti olova u nekim organima kod osoba koje za života nisu bile specifično izložene olovu, Arh. hig. rada, *10* (1959) 217.
9. *Weber, K.:* Primjena fluorescencije, kemiluminescencije i spektrofotometrije u medicini, Arh. hig. rada, *19* (supl. 1) (1968) 135.
10. *Đurić, D., Belamarić, T.:* Normalne vrijednosti porfirina u urinu, Arh. hig. rada, *10* (1959) 221.
11. *Weber, O. A., Valić, F.:* O odnosu koncentracije olova u krvi i koproporfirina u urinu, Arh. hig. rada, *4* (1953) 511.
12. *Mehani, S.:* A Rapid Method for the Determination of Delta Amino-Laevulinic Acid in Urine, Brit. J. Industr. Med., *21* (1964) 78.
13. *Đurić, D.:* Otapanje olova iz glazure zemljanog posuđa, Arh. hig. rada, *9* (1958) 297.
14. *Voloder, Kata:* Određivanje olova u brašnu i žitu, Arh. hig. rada, *9* (1958) 89.
15. *Beritić, T.:* Toksikološko značenje eritrocitnih inkluzija, Arh. hig. rada. *8* (1957) 97.
16. *Beritić, T., Grgić, Z., Širec, Anica:* Iron Containing Blood Cells in Human Lead Poisoning, International Congress on Occupational Health VIII, Helsinki, 1957.
17. *Beritić, T., Vandekar, M.:* Morphologic Changes of Erythropoietic Cells in the Bone Marrow of Workers Exposed to Lead, Atti XI Congr. Intern. Med. Lavoro, Napoli, 1954.
18. *Beritić, T., Vandekar, M.:* Some Observations on the Morphology of Erythropoietic Cells in Human Lead Poisoning, Blood, *11* (1956) 114.
19. *Beritić, T., Hahn, A., Hauptmann, E., Keller, Mira:* Serumsko željezo kod kliničkog otrovanja olovom, II sastanak hig. rada, Zagreb, 1953.
20. *Beritić, T.:* Eritrocitne inkluzije u kliničkoj i eksperimentalnoj toksikologiji, Arh. hig. rada, *19* (supl. 1) (1968) 15.
21. *Simonović, I., Kostial, Krista, Maršić, A.:* The Effect of Metal Ions on the Hypotonic Resistence of Erythrocytes *in vitro*, Bull. Scient., *5* (1960), 80.
22. *Kostial, Krista, Vouk, V. B.:* Lead Ions and Synaptic Transmission in a Sympathetic Ganglion, Brit. J. Pharmacol., *12* (1957) 219.
23. *Kostial, Krista, Lorković, H., Vouk, V. B.:* Acethylcholine Sensitivity of Ganglia and Striated Muscles in Presence of Lead Ions, XIIth International Congress on Occupational Health, Helsinki, 1957, Summaries, Vol. II, p. 94.
24. *Lanecreaux, E.:* Nephrites et arthrite saturnines, Arch. gen. med., Serie VII T6, 2 (1881), 641. (cit. 12).
25. *Leyden, A.:* Ein Fall von Bleivergiftung, Path. Anatomie der Bleilähmung und Bleiniere, Deutsch. med. Wschr., *13* (1883) 185.

26. *Gayler, J.:* Zur Histologie der Schrumpfniere nach chr. Bleivergiftung, Inaug. Dissert., Tübingen, 1887. (cit. 12).

27. *Volhard, F., Fahr, T.:* Die Brightsche Nierenkrankheit, 1914, Julius Springer, Berlin, 1914.

28. *Belknap, E.:* Clinical Studies on Lead Absorption in the Human, III. Blood Pressure Observations, J. Ind. Hyg. Toxicol., *18* (1936) 380.

29. *Mayers, H. R.:* Industrial Exposure to Lead, Occup. Med., *3* (1944) 77.

30. *Radošević, Z., Šarić, M., Knežević Jelena, Beritić, T.:* Klinička zapažanja o djelovanju olova na bubreg, Arh. hig. rada, *9* (1958) 233.

31. *Radošević, Z., Šarić, M., Beritić, T., Knežević Jelena.:* The Kidney in Lead Poisoning, Brit. J. industr. Med., *18* (1961) 222.

32. *Markićević Ana* i sur.: Neobjavljeni podaci

33. *Jamnicki, A., Kilibarda, M., Ilijev, N.:* Zapažanja o promjenama krvnog pritiska kod kronične ekspozicije olovu, Arh. hig. rada, *6* (1955) 23.

34. *Beritić, T., Šarić, M.:* Patofiziologija i klinika saturnizma, Arh. hig. rada, *13* (1962) 45.

35. *Prpić–Majić Danica, Šarić, M., Beritić, T., Keršanc Edita:* Primjena manjih terapijskih doza kompleksona EDTA kod otrovanja olovom, Arh. hig. rada, *16* (1965) 125.

36. *Rieders, F., Dunnington, W. G., Brieger, H.:* The Efficacy of Edathamil Calcium Disodium in the Treatment of Occupational Lead Poisoning, Ind. Med. Surg., *24* (1955) 195.

37. *Prpić–Majić, Danica, Šarić, M., Beritić, T., Keršanc, Edita:* Učinak različitih terapijskih doza kompleksona na kliničke i laboratorijske znakove otrovanja olovom, Arh. hig. rada, *13* (1962) 29.

38. *Belknap, L. E.:* Modern Trends in the Treatment of Lead Poisoning. Occup. Med., *3* (1961) 380.

39. *Beritić, T.:* Ocjena radne sposobnosti kod profesionalnog otrovanja olovom, Arh. hig. rada, *18* (1967) 1.

40. *Weber, O. A., Voloder, Kata:* The Determination of Small Amounts of Mercury in Biological Materials, Arh. hig. rada, *8* (1957) 235.

41. *Fugaš, Mirka, Vouk, V. B., Topolnik, Z.:* Environmental Conditions in the Mercury Mine of Idria, Brit. J. Industr. Med., 7 (1950) 168.

42. *Valić, F., Jacobs, B. M.:* Assessment of Mercury Air Concentrations in Work Environment, Am. Ind. Hyg. Assoc. J., *26* (1965) 266.

43. *Kostial, Krista, Vouk., V. B.:* Djelovanje živinih iona na ganglijsku transmisiju, Arh. hig. rada., *8* (1957) 247.

44. *Vouk, V. B., Kostial, Krista, Hefer B.:* A Comparison of the Effects of Mercury and Lead Ions on Synaptic Transmission, XIIth International Congress on Occupational Health, Helsinki, 1957, Summaries, Vol. II, p. 91, Vol. III, p. 283.

45. *Šimonović, I., Kostial, Krista, Maršić, A.:* Clotting Changes Induced by Metal Ions *in vitro*, Arh. hig. rada, 10 (1959) 227.

46. *Kesić, B., Häusler, Vera:* Hematological Investigation on Workers Exposed to Mercury Vapour, Ind. Med. Surg., *20* (1951) 485.

47. *Njemirovskij, Z.:* Oralni simptomi kod profesionalnog otrovanja živom, Arh. hig. rada, *3* (1952) 463.

48. *Markićević, Ana:* Neobjavljeni podaci.

49. *Cigula, Mira, Vilar, Julia, Valić, F.:* Effect of Inorganic Mercury Exposure on the Activity of Some Serum Enzymes, Proc. XV Int. Congress on Occupational Health, Beč, 1966, A III–23.

50. *Markićević Ana:* Ocjena radne sposobnosti kod profesionalnog otrovanja živom, Arh. hig. rada,*18* (1967) 232.

51. *Vouk, V. B., Topolnik, Z., Fugaš, Mirka:* Respirators for Protection Against Mercury Vapour, Brit. J. Industr. Med., *10* (1953) 69.
52. *Topolnik, Z., Fugaš, Mirka, Vouk, V. B.:* Zaštita radnika u rudniku žive u Idriji, Arh. hig. rada, *3* (1952) 201.
53. *Fugaš, Mirka, Valić, F.:* Onečišćenje industrijske i komunalne atmosfere, Arh. hig. rada, *19* (supl. 1) (1968) 49.
54. *Šlezinger, M.:* Prikaz slučaja manganizma, Lij. vjes., *62* (1940) 361.
55. *Ivančević, I.:* O šibenskom manganizmu, Izvanredna izdanja Inst. za farmakologiju i toksikologiju u Zagrebu, *1* (1941).
56. *Karminski, Đ.:* Nekoji noviji pogledi na problem manganizma s osobitim obzirom na prilike kod nas. Izvanredna izdanja Farm. Inst., Zagreb, Vol. *5* (1949).
57. *Dogan, S., Beritić, T.:* Industrijsko–higijenski i klinički aspekti profesionalnog otrovanja manganom. S prikazom deset slučajeva iz vlastite prakse, Arh. hig. rada, *4* (1953) 139.
58. *Kesić, B.:* Haematological Investigation on Workers Exposed to Manganese Dust, Arch. Ind. Hyg. and Occupat. Med., *10* (1954) 336.
59. *Kostial, Krista, Jurišić, Z.:* Effect of Manganese on Synaptic Transmission, Arh. hig. rada, *7* (1956) 27.
60. *Markićević Ana, Hećimović, A., Mark, B., Beritić, T.:* Rezultati ciljanih pregleda radnika eksponiranih prašini tvrdih metala, Arh. hig. rada, *17* (1966) 55.
61. *Beritić, T., Prpić–Majić Danica, Mark, B., Markićević Ana, Vurdelja Bosiljka:* Pneumokonioza uzrokovana tvrdim metalom, Arh. hig. rada, *14* (1963) 261.
62. *Moschinski, G., Jurich, A., Reinl, W.:* Die Lungenveräu derungen bei Sinterhartmetall Arbeitern, Arch. Gewerbepath., Gewerbehyg., *16* (1959) 697.
63. *Bech, H. O., Kipling, M. D., Heather, J. C.:* Hard Metal–disease, Brit. J. industr. Med., *19* (1962) 239.
64. *Miller, C. W., Dawis, N. W., Goldman, H., Wyatt, P. J.:* Pneumoconiosis in the Tungsten–Carbide Tool Industry, Arch. industr. Med., *8* (1953) 453.
65. *Fairhall, L. T., Castberg, H. T., Carrozzo, N. J., Briton, H. P.:* Industrial Hygiene Aspects of the Cemented Tungsten Carbide Industry, Occup. Med., *4* (1947) 571.
66. *Markićević, A.:* O patogenezi pneumokonioze uzrokovane tvrdim metalom, Tuberkuloza, *19* (1967) 80.
67. *Beritić, T., Stahuljak Dunja:* Nikal, Lij. vjes., *83* (1961) 506.
68. *Markićević Ana:* Nikalni dermatitis. Arh. hig. rada, *11* (1960) 147.
69. *Markićević Ana:* Neobjavljeni podaci.
70. *Kostial Krista, Voloder Kata, Vouk, V. B.:* Utjecaj helatogenih supstancija na retenciju urana u bubrezima, Arh. hig. rada, *13* (1962) 289.
71. *Vouk, V. B., Branica, M., Weber, O. A.:* Note on Polarographic Determination of +6 Uranium, Arhiv kem., *25* (1953) 225.
72. *Weber, O. A., Branica, M., Vouk, V. B.:* Polarographic Behaviour of +6 Uranium in a Mixture of Salicylic and Sulphuric Acid., Arhiv kem., *25* (1953) 235.
73. *Valić, F., Weber, O. A.:* Polarographic Determination of Uranium in Blood, Arhiv kem., *27* (1955) 53.
74. *Voloder, K.:* Polarografsko odredivanje urana u urinu i bubrezima – Neobjavljen rad.