Acta Paediatrica Hungarica 30 (1), pp 143-154 (1990)

MODULATION OF Fcγ RECEPTORS IN THE MEMBRANE OF HUMAN MONOCYTES: EFFECT ON MONOCYTE FUNCTIONS+

J.W. MANNHALTER, H.M. WOLF, J. GÖTTLICHER, R. AHMED and M.M. EIBL

Institute of Immunology, University of Vienna, Vienna, Austria

INTRODUCTION

Opsonization of microorganisms by plasma components (e.g. antibodies, complement) followed by interaction with the respective receptors expressed in the membrane of phagocytic cells (complement receptors as well as receptors for the Fc portion of IgG) generally precede the series of events leading to the elimination of pathogens. Besides their obligatory role in microbial uptake /1/, these ligand-receptor interactions additionally induce a number of signals which regulate immune defense mechanisms. Ligation of Fcγ receptors (FcR), for example, is followed by cellular functions such as release of histaminase and lysosomal enzymes, as well as the respiratory burst, thus mediating ADCC and intracellular killing (2, 3). Because of these important interactions, modes of Fc and complement receptor modulation have attracted considerable attention.

Since previous studies by other groups clearly demonstrated the FcR-modulatory capacity of polymeric IgG (immune complexes, IgG aggregates) (4-6) and since immune complexes have long been known to interfere with macrophage FcR functions in a variety of disease states (7-10), we became interested in the functional consequences of Fc and complement receptor modulation. In the present paper we report briefly on our experience in polymeric IgG-induced immune modulation at the

+Presented at the International Workshop on Phagocytic Cell Disorders, Debrecen, April 24-26, 1988.

Akadémiai Kiadó, Budapest

level of the human monocyte. This report is divided into four parts: (i) effect of polymeric IgG on the expression of Fc and complement receptors in the membrane of human monocytes; (ii) effect of polymeric IgG on monocyte effector functions; and (iii) effect of polymeric IgG on monocyte accessory functions. Finally, this report also includes (iv) preliminary data on lymphokine-mediated reexpression of down-modulated FcR functions.

Effect of polymeric IgG on the expression of Fc and complement receptors in the monocyte membrane

Interference of polymeric IgG with monocyte Fc receptor functions has been shown to occur by different mechanisms: (i) by a blockade of FcR due to surface-bound immune complexes or IgG polymers /11, 12/; (ii) by down-modulation of FcR following interaction with a surface-bound ligand (ligand-specific lateral movement of FcR in the plane of the cell membrane followed by interaction with surface-bound IgG) /13/; and (iii) by long-term down-regulation of FcR due to shedding or ingestion and degradation of the ligand-receptor complex /14/.

In a previous study /15/ we reported on a polymeric IgG-induced down-modulation of human monocyte Fc receptors. This down-modulation could be induced by interaction of human monocytes with soluble IgG aggregates /15/ and with immune complexes (J.W. Mannhalter et al., manuscript in preparation) and was a long-term effect (significantly decreased FcR expression could be observed for up to 5 days after the modulation). Of special interest was the fact that the polymeric IgG-induced FcR down-modulation in the monocyte membrane was accompanied by a concomitant decrease in the expression of the receptor for the complement cleavage product iC3b (CR3), while the expression of other cell surface structures, such as MHC class II, CR1 and microglobulin, remained unimpaired. Details of the modulation technique as well as of the results are given in references 15 and 16; however, for clarification and for better understanding of the results presented in this paper the various steps of the modulation procedure used are summarized in Table I.

TABLE I

Modulation of FcR and CR3 in the membrane of human monocytes: modulation procedure

- Isolation of peripheral blood mononuclear cells by buoyant density gradient centrifugation

- Preparation of a monocyte monolayer by adherence to plastic petri dishes

- Treatment of monocytes with the modulating agent (IgG aggregates, immune complexes, opsonized zymosan) for 1 hr at 37°C

- Removal of unbound ligand by multiple washing steps followed by incubation at 37°C for 16 hrs

- Determination of FcR and CR3 expression (by rosetting techniques, radioligand binding or by using receptorspecific monoclonal antibodies) and assessment of monocyte functions (receptor-mediated phagocytosis, oxydative burst and intracellular killing, antigen presentation)

In a recent publication (16, to be published in the November 15, 1988 issue of the Journal of Immunology) we also addressed the question of the type of Fc receptor modulated. Human monocytes express two types of Fc receptors (reviewed in 17), FcR I (Mr 72 kD), a high-affinity receptor interacting with both monomeric and polymeric IgG, and Fcr II (Mr 40 kD), a low-affinity receptor interacting predominantly with IgG polymers and immune complexes. The third FcR present on human leukocytes (FcR III or FcR_{10}, Mr 50-70 kD) is not expressed in the membrane of freshly isolated monocytes, but appears after cultivation for 10 to 12 days /18/. Our results published in reference 16 clearly demonstrate that the type of FcR modulated by polymeric IgG is FcR II. Since a concomitant modulation of FcR and CR3 was induced after treatment of monocytes with IgG polymers (by triggering the Fc receptor), we checked for a possible co-modulation of FcR and CR3 after triggering the receptor for the complement component iC3b. Indeed, interaction of monocytes with opsonized zymosan (ligand CR3 /19/) led to a down-modulation of CR3, and this was accompanied by a decrease in FcR binding capacity (as assessed by reduced binding of IgG-coated red blood cells). However, the type of FcR modulated in this case was FcR I. The results of these studies are shown in Tables II and III.

These results suggest that interaction of a specific receptor with its ligand not only changes the expression of the receptor triggered, but also has a modulating effect on other functionally important membrane structures. Our studies also indicate that the types of receptor co-modulated appear to be dependent on the species of receptor triggered.

Effect of polymeric IgG on effector function of human monocytes

Since interaction of monocytes with IgG polymers as well as with immune complexes led to a decrease in the expression of FcR and CR3, we asked the question whether down-modulation of these receptors also affected cellular functions. With respect to effector functions it has been shown by several groups, including our own /12, 15, 20/, that down-modulation of FcR resulted in a decrease in the capacity of the cells to phago-

TABLE II

Effect of polymeric IgG on FcR expression of human monocytes

	SMFI		% of control	(modulation)
	DPBS	polymeric IgG		
FcRI (32.2)	88.6	93.9	105.9	n.m.[+]
FcRII (IV.3)	312.4	157.2	50.3	(-49.7%)
FcRII (2E1)	188.4	68.2	36.2.	(-63.8%)

Monocyte monolayers were incubated for 1 hr in the presence of Dulbecco's PBS (DPBS) alone or DPBS containing 10 mg/ml of polymeric (heat-aggregated) human IgG. After washing, the cells were further incubated for 16 hrs in complete medium before the expression of FcRI (with mAb 32.2) and FcRII (with mAb IV.3 and 2E1) was examined by flow cytometric analysis in indirect immunofluorescence. Specific mean fluorescence intensity (SMFI) for the respective mAb was calculated by subtracting the mean fluorescence intensity of cells stained with FITC-conjugated anti-mouse immunoglobulin (GAM-FITC) alone. Results of one representative experiment out of four experiments are given.

[+] n.m. = non-modulatory.

TABLE III

Opsonized zymosan induces a specific down-regulation of monocyte CR3 and FcRI

	% fluorescent-positive cells		% of control	(modulation)
	DPBS	opsonized zymosan		
CR3 (Mol)	90	54.4	60.4	(-39.6%)
FcRI (32.2)	79.1	24.9	31.5	(-68.5%)
FcRII (IV.3)	93.6	85.9	91.8	n.m.+
FcRII (2E1)	93.4	79.6	85.2	n.m.+

Monocyte monolayers were incubated for 1 hr in the presence of Dulbecco's PBS (DPBS) alone or DPBS containing 250 µg/ml of serum-opsonized zymosan. After washing, the cells were further incubated for 16 hrs in complete medium before the expression of β_2m (with mAb L368), FcRII (with mAb IV.3 and 2E1) and FcRI (with mAb 32.2) was examined by flow cytometric analysis in indirect immunofluorescence. Results of one representative experiment are shown. Data are expessed as the percentage of fluorescent-positive cells stained with the experimental mAb minus the percentage of cells stained with the second-step reagent (GAM-FITC) alone.

+ n.m. = non-modulatory.

cytose IgG-coated particles. In addition, we were able to demonstrate /15/ that the polymeric IgG-induced decrease in the expression of FcR and CR3 was accompanied by an impaired ability of such monocytes to generate O_2-radicals upon stimulation with serum-opsonized zymosan (known to trigger CR3 /19/) or IgG aggregates (interacting with FcR). As a consequence thereof, polymeric IgG treatment also significantly reduced the monocytes' capacity to kill an E. coli strain (E. coli 089:H10) which requires opsonization by both antibodies and complement for proper elimination /21/. The results of these studies are summarized in Table IV.

Effect of polymeric IgG on monocyte accessory functions

Decreased accessory functions of mononuclear phagocytes after interaction with IgG polymers have been recently reported in the mouse system /22, 23/. Interaction of mouse peritoneal macrophages with surface-bound immune complexes resulted in an impairment of these cells' antigen-presenting capacity, an effect that could be attributed to an inability to express Ia-like antigens (coupling of processed antigen to Ia is one of the prerequisites for antigen presentation /24, 25/. We investigated the influence of polymeric IgG treatment on antigen presentation in the human system /26/ and found a similar effect. The capacity of IgG polymer-treated monocytes to present antigen to autologous T cells was found to be severely impaired (between 18% and 36% of the control); it was not, however, accompanied by decreased expression of Ia (MHC class II) antigens. In contrast to resting mouse macrophages, virtually all of the abherence-purified human monocytes express MHC class II, and our data clearly demonstrated an absence of polymeric IgG-induced down-regulation of MHC class II already expressed in the monocyte membrane /26/. However, an effect on newly expressed Ia or on the kinetics of Ia expression cannot be ruled out at present.

Reexpression of FcR binding function

In our previous studies we were able to show that pretreatment of human monocytes with IgG polymers (immune

TABLE IV

Polymeric IgG-induced changes in monocyte effector functions

Monocyte function studied	Changes after pretreatment
FcR-mediated phagocytosis[a)]	Reduced by 50%
Generation of O_2-radicals[b)]	Reduced by 64% (zymosan-triggered, receptor CR3) Reduced by 67% (IgG aggregate-triggered, receptor FcR)
Microbial killing[c)]	Reduced between 44% and 71%

a) Measured by ingestion of IgG-coated ox red blood cells.
b) Determined by luminol-enhanced chemiluminescence
c) Assessed by killing of E. coli 089:H10.

TABLE V

Reexpression of monocyte FcR after down-modulation by immune complexes

Pretreatment	Immune complexes % RFC (AI)	DPBS % RFC (AI)
Medium	16±9 (0.93±0.29)	81±4 (3.92±0.77)
MLC supernatant	70±3 (2.92±0.13)	78±2 (3.78±0.44)

Monocyte monolayers were pretreated for 1 hour with tetanus toxoid/TAT immune complexes. After removal of unbound ligand by washing, the cells were incubated in medium for 16 hrs. Then lymphokine-rich MLC supernatant (10%) or medium was added, followed by a 6-hr incubation step. Receptor binding function was determined by examining rosette formation of monocytes with IgG-coated ox red blood cells. Results are expressed as percentage of rosette-forming cells (% RFC) and attachment index (AI, average number of erythrocytes bound per monocyte) in parentheses and represent $\bar{x} \pm$ SD of 6 experiments.

complexes, IgG aggregates) led to a down-modulation of FcR and CR3 which was accompanied by an impairment of monocyte effector and monocyte accessory functions. The next logical question to ask was: is it possible to reexpress the down-modulated receptors and does reexpression of the receptors result in a reappearance of the impaired cellular functions? Since lymphokines (γ interferon as well as the various interleukins) are known to have a profound effect on receptor expression, we first cultured the polymeric IgG-pretreated monocytes in the presence of lymphokine-rich mixed lymphocyte culture (MLC) supernatant. MLC supernatant was added to the cultures upon completion of the receptor modulation procedure, and as can be seen in Table V, reexpression of FcR binding function (as assessed by adherence of IgG-coated erythrocytes) was observed after an incubation period of 6 hours. However, this kind of treatment did not lead to a reexpression of CR3 (data not shown). The type(s) of lymphokine(s) responsible for reexpression of FcR binding function have yet to be elucidated. However, the data obtained so far suggest that expression of FcR and CR3 is controlled by different mechanisms.

CONCLUDING REMARKS

Circulating immune complexes have long been considered to profoundly affect host defense mechanisms against invading pathogens and to modulate cellular interaction required for an appropriate course of the immune response. The presence of circulating immune complexes has been shown to render mice more susceptible to infections with an intracellular pathogen /22, 23/, and patients with hemophilia A, a patient population with increased immune complex serum levels, display a decreased resistance to obligatory intracellular microorganisms as well /27/. Immune defense mechanisms for these types of infection require properly functioning phagocytes, and an impairment of mononuclear phagocyte functions could at least partially explain the increased susceptibility to infections. In this

context it is interesting to note that monocytes isolated from the peripheral blood of hemophiliacs frequently show a reduced expression of FcR (J.W. Mannhalter and M.M Eibl, unpublished data), and a defect in monocyte accessory function (reduced antigen-presenting capacity) has been described in this group of patients /28/.

By employing human monocytes as a model system, we showed that interactions of IgG polymers with phagocytic cells led to a decrease in the expression of functionally important cell surface components (FcR, CR3) which was accompanied by an impairment of monocyte functions. It therefore appears likely that IgG polymers as well as immune complexes interfere directly with host defense mechanisms by down-modulating effector functions and in addition exert a regulatory effect on the immune response by interacting at the level of accessory cell - T cell cooperation.

REFERENCES

1. Unkeless JC, Wright SD: In: Snyderman R ed. Contemporary Topics in Immunobiology, Vol. 14, Regulation of Leukocyte Function, pp. 171-187. Plenum Press, New York and London 1984

2. Dorrington KJ: Immunol Communications 5: 263, 1976

3. Johnston RB Jr, Lehmeyer JE, Guthrie LA: J Exp Med 143: 1551, 1976

4. Rabinovitch M, Manejias RE, Nussenzweig V: J Exp Med 142: 827, 1975

5. Mellman I, Plutner H, Steinman RM, Unkeless JC, Cohn ZA: J Cell Biol 96: 887, 1983

6. Michl J, Unkeless JC, Pieczonka MM, Silverstein SC: J Exp Med 157: 1746, 1983

7. Turner RA, Schumacher HR, Myers AR: J Clin Invest 52: 1632, 1973

8. Frank MM, Hamburger MI, Lawley TJ, Kimberly RP, Plotz PH: N Engl J Med 300: 518, 1979

9. Lockwood CM, Worrledge S, Nicholas A, Cotton C, Peters DK: N Engl J Med 300: 524, 1979

10. Hamburger MI, Moutsopoulos HM, Lawley TJ, Frank MM: Ann Intern Med 91: 534, 1979

11. Huber H, Weiner M: In: Wagner WH, Hahn H eds. Activation of Macrophages, p.54. Excerpta Medica, Amsterdam 1974

12. Kurlander RJ: J Clin Invest 66: 773, 1980

13. Michl J, Pieczonka MM, Unkeless JC, Bell GI, Silverstein SC: J Exp Med 157: 2121, 1983.

14. Mellman I, Plutner H: J Cell Biol 98: 1170, 1984

15. Mannhalter JW, Ahmad R, Wolf HM, Eibl MM: Int Arch Allergy Appl Immunol 82: 159, 1987

16. Wolf HM, Mannhalter JW, Salzmann HC, Göttlicher J, Ahmad R, Eibl MM: (J Immunol 141, in press) 1988

17. Anderson CL, Looney RJ: Immunol Today 7: 264, 1986

18. Clarkson SB, Ory PA: J Exp Med 167: 408, 1988

19. Ezekowitz RAB, Sim RB, MacPherson GG, Gordon S: J Clin Invest 76: 2368, 1985

20. Griffin FM Jr: J Exp Med 152: 905, 1980

21. Eibl M: In: Dierich MP, Füst G, Turner MW eds. Triggering of Phagocytic Cells, pp. 239-247. Medicina Publishing House, Budapest, 1980

22. Virgin HW IV, Unanue ER: J Immunol 133: 104, 1984

23. Virgin HW IV, Unanue ER: Ann N Y Acad Sci 437: 16, 1984

24. Babbitt BP, Allen PM, Matsueda G, Haber E, Unanue ER: Nature, Lond 317: 359, 1985

25. Allen PM, Matsueda GR, Haber E, Unanue ER: J Immunol 135: 368, 1985

26. Mannhalter JW, Ahmad R, Pinzker H, Wolf H, Eibl MM: Clin Immunol Immunopathol 39: 491, 1986

27. Beddall AC, Hill FGH, George RH, Williams MD, Al-Rubei K: J Clin Pathol 38: 1163, 1985

28. Mannhalter JW, Zlabinger GJ, Ahmad R, Zielinski CC, Schramm W, Eibl MM: Clin Immunol Immunopathol 38: 390, 1986

Acta Paediatrica Hungarica 30 (1), pp 155-161 (1990)

BOOK REVIEWS

Berner Data in Paediatrics (in German); third edition: Gustav Fischer Verlag, Stuttgart - New York, 1988. 702 pages.

This third edition has been largely rewritten. Its 24 chapters offer firm basis for everyday paediatric practice; the last chapter contains the reference values.

The book describes:

- the most important diagnostic tasks, functional procedures, interpretation of results (in tables),
- modern drug therapy of all important diseases (antibiotics, hormones, cytotoxic drugs, etc.)

in detail.

The book has been edited three times within four years; this proves its popularity and usefulness. Each paediatrician governing the German language should keep it on his shelf.

It is a paperback produced by photoprint technique, which secures its reasonable price.

Miklós Miltényi M.D.

Paul Imbach: Datenbuch der pädiatrischen Onkologie

As a result of progress in paediatric oncology made during the last fifteen years about half of children afflicted by malignant disorders are healed. The favourable results can be ascribed to better diagnostic procedures, to new drugs and to new therapeutic approach organized within national and international programs. Both diagnosis and therapy can be only improved by team work; the team comprises the paediatric oncologist, surgeon, radiologist, pathologist, psychologist, social worker, paediatrician of the hospital nearby the patient's home and the general practitioner. It is inevitable that all these experts possess the knowledge about the exact nature, diagnosis, therapy and prognosis of these diseases. This booklet serves this aim.

Doctor Imbach's aim is not to give a detailed and deep review on paediatric tumours. He does not offer sophisticated

Akadémiai Kiadó, Budapest

treatment protocols, rare case histories but gives a concentrated description of the most important topics of tumours occurring in children. He does not deal with chapters otherwise amply discussed in books on paediatric oncology, e.g. mode of action of cytostatic drugs, the importance of chromosomes and oncogens or psychologic care of patients. Instead he offers concise lists of aetiology, diagnostic procedures, differential diagnosis, therapy and prognosis of each important paediatric tumour. In spite of its abbreviating style the book contains even the most up-to-date data of the field; it can be recommended to all doctors having an interest in the specialty, beginners included.

Dezső Schuler M.D.

Eric Taylor: The hyperactive child. Recommendations for parents and children (in German). Hippokrates Ratgeber, Hippokrates Verlag, Stuttgart, 1986. 102 pages. ISBN 3-7773-0800-5

The author, a reknown expert of clinical epidemiological aspects of hyperactivity, is leader of the psychiatric department for children and adolescents, Maudsley Hospital, London.

A rather large number of recent studies of high scientific standard have thrown new light to some problems around hyperactivity. Within the discussion of recent knowledge, the author offers a critical review in popular form, focusing on practice. In his opinion, the hyperactive child and its parents are a case or emergency. The most useful element in this book is the detailed description of the facilities and methods accessible in the United Kingdom, literally showing the way for parents and teachers of hyperactive children.

Thus, the principal aim of the work is to give information in a popular style. First of all, general issues are touched: definition, diagnosis, differential diagnosis, overlapping with other terms (minimal brain dysfunction, attention deficit disorder, etc.) are dealt with.

All possible causative factors of hyperactivity are reviewed in a detailed chapter: they may be of biological, genetic,

psychogenic or organic nature; ample attention is paid to long-term exposition to lead: concise information is - quite laudably - offered to the lay reader possibly confused by overwhelming and contradictory data pourred out by mass media. The author stresses prevention of exposure to lead (lead-free fuel, drinking water and paints, etc.), denying the justification of treatment of alleged lead poisoning, a diagnosis often poorly confirmed.

In addition to school problems, the issue of family environment is largely discussed. In nearly all cases there are some tasks for the parents: a good many pieces of practical advice are given for self-supporting groups. The role of alleged dietary factors is elucidated, in the author's mind they are of no major importance. In addition to describing the various modes of self-supporting, the author gives valuable advice about what types of institutions and experts can be approached in Western Europe with the problem of childhood hyperactivity. In the ideal case, a team consisting of experts in special teaching, logopaedics, audiology, behavior therapy, care and, eventually, gymnastics should be available. Drug treatment and psychotherapy are shortly discussed.

The beautiful book contains a broad spectrum of knowledge useful for parents and teachers caring hyperactive children and willing to deepen their knowledge on certain issues. It can also be recommended to medical students and young doctors showing affinity to these problems.

Viktor Farkas M.D.

P. Grossmann, W. Plennert (editors): Paediatrics. Volume 3 (in German). Georg Thieme, Leipzig, 1986.

The third volume of three is also dedicated to the main aim of this textbook: to preserve the unity of paediatrics.

In this volume 10 organ oriented chapters deal with the remaining issues: infectious diseases, diseases of the respiratory system, heart, eyes, skin and kidneys, accidents, paediatric surgery and dentistry, history of the specialty paediatrics.

As in the two previous volumes the text keeps in mind the laws, rules, habits and facilities in the German Democratic Republic, offering a panorama of diagnostic and therapeutic tools available in that country and all over the world.

The chapter of infectious diseases does not go much into detail because a textbook of infectology has recently been published in the GDR. Only the most important general knowledge is reviewed, the issues tropical diseases and development and disorders of the immune system are included.

Each chapter is introduced by data of embriology, anatomy and physiology, underlining the characteristic features of childhood. Also, epidemiology and incidence of several disorders, illustrated by own or adopted data, are presented; a detailed list of references helps the reader to additional information at the end of each chapter.

The figures, tables and photograms are instructive, comprehensible, of good quality, illustrating the text in an excellent way.

The structure of the volume is clear, making it easy to read and to follow. This is further enhanced by a very good list of contents and a subject index.

In summary, the third volume of this textbook of paediatrics nicely represents the specialty practised and investigated in the German speaking countries. It should be read by medical students, future paediatricians and by all doctors treating children and needing extended knowledge in this field.

Károly Schmidt M.D.

L. Lugosi and W. Hennessen (editors): International Symposium on BCG Vaccines and Tuberculins. Akadémiai Kiadó, Budapest, 1986.

The two volumes comprise the papers read at the congress of International Association of Biological Standardization (IABS) held in Budapest, September 6-9. 1983. This means a publication delay of six years, an information anomaly deplorable even with an ever-green issue like that. The conference in the Hungarian capital was organised as a memory of the 50th anniversary of Calmette's (1863-1933) death; the date coincided

with the 70th return of the year of Frigyes Korányi's (1827-1913) death, initiator of the organised antituberculosis combat in Hungary. The book is the 58th volume of the series Developments in Biological Standardization, edited by S. Karger (Basle).

In the foreword, Professor Hennessen mentions the fact that Hungary was one of the first countries introducing BCG vaccination at a national level and that the epidemiological data of this country proved the efficacy of the method at a very early time.

The first volume deals with BCG vaccination, tuberculin is the topic of the second volume. About 120 papers from 30 participating countries and their discussion material can be found here.

H.G. ten Dam (Geneva, Switzerland) states in his review that BCG vaccination of young infants will be indicated still for a very long time to come. We are reminded that the generalised forms of childhood - miliary tuberculosis and basilar meningitis - are only scarcely associated with positive sputum cultures, their diagnosis is often delayed. Vaccination of neonates is relatively cheap. From the review and especially from the subsequent discussion it clearly turned out that in spite of BCG vaccination programs delivered for several decades only few controlled studies unequivocally confirming the protective effect of the vaccine are available. The three studies withstanding thorough scrutiny (on US Indians, infants of Chicago, English schoolchildren) confirm a protective effect of BCG of about 75 %.

Lugosi presents Hungarian data. Facultative vaccination with the strain Budapest started in 1933, vaccination has been compulsory since 1954. New strains (Paris 1102, Seed-Lot P 1173) were introduced in 1960. As a result of the total primo- and revaccination program the incidence of childhood tuberculosis fell from 250 to 1/100000 between 1959 and 1982. Still, the risk of exposure during childhood is rather high since the prevalence of Koch positivity is 21-32/100000 among adults.

Several sections dealt with the microbiological properties of BCG vaccines, problems of production, quality control and standardisation.

Epidemiological data from certain regions pointed to a reduced protective power of the vaccine under hot climate; in fact, the BCG vaccination program of 1979 in South India proved to be hardly effective. This cannot exclusively be ascribed to social factors since a similar phenomenon had been encountered in the well-to-do subtropical parts of Australia. Several experts think that in those regions only neonatal vaccination is justified.

The second volume contains the papers concerning tuberculins. Reports from various countries show that infection with mycobacteria causing no tuberculosis is spreading and, as a consequence, the number of false positive reactions may be very high, e.g. in Delft (The Netherlands).

Studies on primary school children between 1966 and 1980 had demonstrated a decrease in human sensitivity from 1.3 % to 0.8 %, the positive reactions against PPD scrophulaceum increased from 4 to 13.3 %. In Poland, practically no cause of non-specific tuberculin sensitivity was found in 1966; in 1983 a percentage as high as 5.1 % was seen.

Some authors think that infection with atypical mycobacteria leads to natural resistance to tuberculosis: the level of immunisation, however, does not attain the power of BCG vaccination.

There is general agreement in that the Mantoux-test is correct basis of tuberculin diagnostics but there is a need for simpler, less painful techniques of tuberculin contact. The "monotest" - tuberculin is placed to miniature lancets pressed then onto the skin - can transmit a quantity corresponding to as much as 5 TU. Some other experts observed an incidence of false negative results as high as 23-64 %.

The volumes printed on a total of 763 pages offer an excellent review on the problems concerning BCG vaccination and tuberculin reactions. The text is copiously illustrated by figures and tables. At the end of the second volume short,

conclusive summaries of each section help the reader. The list of participants and the subject index are equally valuable.

Endre Cserháti M.D.