Elsevier has created a **Monkeypox Information Center** in response to the declared public health emergency of international concern, with free information in English on the monkeypox virus. The Monkeypox Information Center is hosted on Elsevier Connect, the company's public news and information website.

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Poxvirus infections

In a vehicle carrying two children with smallpox, Ali Maow Maalin, a cook at the Merca Hospital in Somalia, contracted the last endemic smallpox infection on the 12th of October 1977 while directing the vehicle from the hospital to the leader of the local smallpox surveillance team (Deria et al., 1980).

Smallpox has for thousands of years been a most feared disease. It has left its marks on the 3000 year old mummy of Ramses V and it was the deadly cargo of the conquistadore ships landing in Mexico. The successful global vaccination campaign resulted, in 1977, in the last natural case of smallpox. Three years later WHO officially declared that smallpox had been completely eradicated from the earth. The smallpox virus is still present in a few freezers in special designated laboratories. The eradication of smallpox will be described at some length as the first, but hopefully not the last, example of an eradication of a severe human disease. The virology of the poxviruses has been reviewed by Joklik (1966), Baxby (1977), Moss (1978), Fenner (1979), and smallpox was recently reviewed by Behbahani (1983).

15.1. The viruses

Poxviruses are the largest and most complicated viruses of humans and they more resemble ‘reduced’ bacteria than viruses. Fig. 15.1 shows the vaccinia virus, which is structurally very similar to smallpox virus (variola). The virions are brickshaped or ovoid, 300–450 nm × 170–260 nm and have both an envelope and a coat enclosing lateral bodies and a core structure. The core structure contains a dsDNA with a M.W. of 85–240 × 10^6. The G + C content is very low, about 36% for vac-
Fig. 15.1. Pox virus. The bar represents 500 nm in this EM picture. (courtesy of Dr. L. Svensson.)

| Genus          | Virus                                    |
|----------------|------------------------------------------|
| Orthopoxvirus  | Smallpox (variola)                       |
|                | Vaccinia                                 |
|                | Monkeypox                               |
|                | Cowpox                                  |
| Parapoxvirus   | Orf                                      |
|                | Milkers nodes                            |
|                | Molluscum contagiosum                    |
cinia virus DNA. The genetic material is enough to code for a few hundred proteins, and more than one hundred have been detected. As shown in Table 15.1 there are poxviruses from three genera infecting humans. Cowpox and monkeypox viruses are orthopoxviruses which also can infect humans. The virions contain 10 major antigens of which one cross-reacts with most poxviruses. There is also extensive serological cross-reactivity within each genera of poxvirus. Although vaccinia and variola virions differ in only one antigen, the restriction enzyme cleavage maps of their DNAs differ.

The relatedness and also important differentiations between variola, monkeypox and vaccinia have been analyzed at DNA level (Esposito et al., 1978). The virus-induced polypeptides can also be analyzed in order to identify poxviruses (Harper et al., 1979). The laboratory differentiation between variola, monkeypox, vaccinia and cowpox is especially important since they can cause similar symptoms.

15.2. Replication and molecular biology

The poxviruses generally have a narrow host range. After penetration into a cell the virus particles are degraded in several steps and the viral DNA is released in the cytoplasm. This process requires the synthesis of viral proteins. The poxvirions contain a DNA dependent RNA polymerase and this enzyme transcribes about 14% of the genome, resulting in the synthesis of viral proteins necessary for the uncoating of the viral DNA. The viral DNA replicates and is transcribed in the cytoplasm. The two DNA strands are linked covalently at both ends.

Many enzymes participate in the poxvirus replication and several are probably virus coded, such as a DNA dependent RNA polymerase (transcriptase), a DNA polymerase, a poly A polymerase, a thymidine kinase, a DNase, a DNA ligase and enzymes required for the capping of viral mRNA. Enzymes induced by vaccinia virus are listed in Table 15.2. The number of viral proteins made is not known, but more than 100 have been found in virions (Essani and Dales, 1979). Extensive modification of virus proteins occurs such as glycosylation, phosphorylation and proteolytic processing. Mature virus particles are released from microvilli or by cellular disruption. Genetic recombination can occur within genera.

15.3. Clinical aspects

Smallpox (Variola)

This has probably been the most devastating disease in history and can be traced back as long as 5000 years in Asia. It is now, fortunately, only of historic interest. The virus is spread by airborne droplets from an infected person to the upper airways of another person. The incubation time is 12–13 days and the virus spreads
TABLE 15.2.
Vaccinia virus enzymes

| Enzyme                                      | Reference                         |
|---------------------------------------------|-----------------------------------|
| (Guanine-7)-methyltransferase               | Boone et al. (1977)               |
| Ribose-2'-O-methyltransferase               | Boone et al. (1977)               |
| Protein kinase                              | Paoletti and Moss (1972)          |
| Thymidine kinase                            | Kates and McAuslan (1967)         |
| DNA dependent RNA polymerase                | Citarella et al. (1972)           |
| DNA dependent DNA polymerase                |                                   |
| Poly A polymerase                           |                                   |
| Guanylyltransferase                         |                                   |
| Endoribonuclease                            | Paoletti and Lipinskas (1978)     |
| DNase                                       |                                   |
| Alkaline protease                           | Arzoglou et al. (1979)            |
| Nucleoside triphosphatase                   | Paoletti et al. (1974)            |
| Polynucleotide 5' triphosphatase            | Tutas and Paoletti (1977)         |
| Polynucleotide ligase                       | Sambrook and Shatkin (1969)       |
| DNA nicking-closing enzyme                   | Bauer et al. (1977)               |

from the mucosa to lymph nodes, resulting in a viraemia. The acute disease is characterized by fever, headache and fatigue and followed by the formation of vesicles. In contrast to varicella (Chapter 13), the vesicles in a smallpox patient develop all at the same time. In surviving patients the vesicles crust and the crusts are lost after about three weeks of disease. Characteristic scars remain after the disease. The mortality varied from 1 to 40% in different parts of the world depending on different subtypes of smallpox. Variola major giving the more severe disease and Variola minor (alastrim) the less severe. Several epidemics were devastating, such as that in Iceland in 1707 when 36% of the total population died in a single year. The fatality rates for some countries are shown in Table 15.3.

Orf virus infection
This is caused by a virus normally infecting sheep. Persons in contact with sheep can be infected and often the orf infection appears as a single lesion on the hands or on the face. The lesion heals in about one month. No virus specific prophylaxis or treatment is available, but there is a vaccine for sheep.

Milker's nodes
This bovine poxvirus differs from cowpox but can also be transmitted to persons handling cows. The symptoms are similar to those of an orf virus infection. The lesions heal without scar in about one month. No specific vaccine or antiviral drug has been reported.
TABLE 15.3.
Case-fatality rates for smallpox in different geographic areas

| Country   | Years     | No. of cases | No. of deaths | Fatality rate (%) |
|-----------|-----------|--------------|---------------|-------------------|
| India     | 1974-1975 | 2 826        | 575           | 20.3              |
| Vaccinated|           |              |               | 6.2               |
| Unvaccinated|          |              |               | 26.5              |
| West Africa| 1967-1969 | 5 628        | 540           | 9.6               |
| Ethiopia  | 1972-1974 | 21 250       | 243           | 1.1               |
| Botswana  | 1972      | 1 059        | 2             | 0.2               |

Data are from the World Health Organization.

*Molluscum contagiosum*

The infectious agent for this disease is an unclassified poxvirus with a world-wide distribution. It is spread by contact and can infect skin and mucous membranes. The transmission is often venereal in adults. After an incubation period of a few weeks, small papules form and grow to about 10 mm in 2–3 months and then regress in about half a year without scar formation. No vaccine or antiviral drug has been reported.

*Monkeypox*

This monkey virus can infect humans and occasional cases are reported in Africa. The symptoms resemble smallpox but the secondary spread among humans is fortunately less efficient, with attack rates of about 4% in contrast to smallpox with attack rates of about 40%. Immunization with vaccinia gives good protection.

*Cowpox*

This virus can spread from cattle to the hands or arms of persons handling cattle. The symptoms resemble a primary vaccinia vaccination. The virus differs both from vaccinia virus and milkers nodes virus, but it is antigenically related to vaccinia.

15.4. Global eradication of smallpox

Several biological features of the smallpox virus itself favoured the final successful attempt to eradicate smallpox, including the absence of an animal reservoir, and absence of any recurrent infections in man, together with an effective and stable vaccine. The WHO intensified the smallpox eradication programme following a suggestion in 1958 by the USSR at the Eleventh World Health Assembly. WHO co-ordinated world-wide efforts from 1966 onwards and provided the expertise, finance (5% of WHO's budget in the early years) and continuing stimulus which were
all required to bring about the final demise of this notorious infection. In that year, for example, 46 countries recorded 131,697 smallpox cases although this probably represented as little as 1% of the real number of cases. Four endemic areas were present namely, Africa, Asia, Indonesia and Brazil. Large financial contributions were made initially by the USSR and USA but eventually 26 countries became contributors. By 1973, 80% of the smallpox vaccine was being produced in the endemic countries and another advance came in 1968 when the bifurcated needle was introduced, soon becoming the standard method for vaccination. Fenner (1982) has recently summarized the problems of vaccination in two of the most difficult countries, namely Ethiopia and India and he has emphasized how the lessons learnt could be applied when other diseases such as measles or polio become, in their turn, the next in line for eradication. These lessons encompass knowledge of the biology of the virus, foibles of human nature, technology and mass communication and exertion. An interesting observation made is that links between field workers and researchers were, contrary to general opinion, essential for the final eradication campaign. Thus, the laboratories were able to develop more rapid and accurate diagnostic methods, and continuing research also solved some essential unsolved problems such as whether monkey pox could mutate to variola. Restriction endonuclease analysis of genomes of strains of orthopoxvirus, monkey poxvirus and white pox mutants showed no evidence that these viruses could mutate or revert to variola.

Biologically, eight features of smallpox favoured its eradication (Table 15.4). Importantly, the general severity of the disease justified a major effort to eradicate the virus. Throughout the world and over the centuries only one serotype of smallpox has ever been identified and, moreover, orthopoxviruses all cross react serologically. A heat stable freeze dried vaccine was developed in the early 1950s by L. Collier at the Lister Institute, thus obviating the need for refrigeration and ‘cold chains’. Potency was retained for periods of greater than 1–2 months at 37°C and the vaccine was very cheap. All vaccine was donated or produced locally. The smallpox virus was furthermore restricted to humans, with no animal reservoir (unlike influenza or arboviruses, for example, Chapters 7 and 5). It was also an important

| TABLE 15.4. |
| Biological features of smallpox that favoured its eradication |
| 1. Severe disease |
| 2. No subclinical cases |
| 3. Infectivity accompanies rash |
| 4. Recurrent infectivity unknown |
| 5. Only one serotype |
| 6. Availability of an effective stable vaccine |
| 7. Seasonality |
| 8. No animal reservoir |
factor that subclinical smallpox did not occur in unvaccinated individuals and that patients did not spread the disease during the incubation period (unlike measles, polio and influenza). Smallpox is not as contagious as measles, chickenpox or influenza and transmission required a closer contact with patients. The average smallpox case did not infect more than 2 or 3 other people. If patients who had smallpox were surrounded by vaccinees or immune persons the chain of transmission was broken. Finally, unlike herpes virus or hepatitis B virus for example, carrier states or latency were unknown with smallpox.

Many invaluable lessons can be learnt from the smallpox eradication campaign and Fenner (1982) highlights the most important of these. Success of a vaccination programme should not be estimated solely in terms of number of vaccinees because many vital groups may be left out e.g. newborn babies. Also it was not considered possible to vaccinate all 650 million people in India. Mass vaccination had to be combined with surveillance and containment. Therefore available resources were concentrated on areas with smallpox cases. Moreover, the reporting system had to be accurate. Identification of smallpox and containment of foci rather than 100% vaccination was the key strategy. To give an idea of the scope of the operation in India, in 1974, 100 epidemiologists were in the field at any one time, and at this period there were 8403 individual outbreaks with 11 000 cases of smallpox. 28 mobile teams were established in addition to 2800 field workers. A searcher enquiring about smallpox became a familiar figure in every village and rewards were offered for notification of cases. Smallpox patients were removed by flying squad to infectious diseases hospitals and neighbours vaccinated. Fortunately, identifying the disease needed no great diagnostic skill. 'Search weeks' were initiated and teams visited every household to break the chain of transmission. By May 1975 the disease had been conquered in India. A major task had been overcoming ignorance and prejudice. For example, so rooted was smallpox in the everyday life of India that the disease had its own Goddess, Shitala Mata (Fig. 15.2). Temples dedicated to the smallpox goddess are dotted around the country and it was believed that she spilled grain from a basket on her head every time she shook it and each grain turned into a smallpox pustule. Victims survived if she used water from the pitcher in one hand to clean the spilt grain, but did not survive if she used the broom which was in the other. Some people worshipped smallpox cases as being blessed by the goddess and so spread the infection.

Ethiopia illustrated other problems. Most of the 28 million inhabitants lived in rural areas and communication was poor, with most trained health people in the urban areas. Half the population lived more than a day's walk from any accessible road. Civil war and famine compounded the problems. Moreover, variola minor, the endemic type of smallpox, was not considered to be a major national public health problem in Ethiopia itself. Initially emphasis was placed in surveillance, notification and containment and so it is not surprising that reported cases rose from 722 in 1970 to 26 329 in 1971. Introduction of more vehicle transport (Fig. 15.3)
and helicopters meant that by 1975 containment was feasible throughout the whole country and by 1976 the disease had been conquered. For two further years teams worked to ensure no cases had been missed. In many countries a reward was offered and tens of thousands of cases of chickenpox, measles and other rash diseases were
reported by villagers in hopes of collecting a reward. Thousands of specimens were sent to the WHO diagnostic centres is Moscow (USSR) and Atlanta (USA) but none proved to be smallpox.

The eradication programme also illustrates dramatically how important were political and social conditions and D.A. Henderson, director of the campaign between 1967 and 1976, has emphasized that the success of many national programmes often ‘hung by a thread’. During the first 4 years of the West African programme there were 23 changes of government in the 18 countries. “Smallpox eradication was achieved but was just barely achieved.” The final success can be illustrated by Fig. 15.4 which shows the cover of the World Health of May 1980 announcing that smallpox is dead and by Fig. 15.5 one of the pages from that issue summarizing the achievement, and emphasizing how little this campaign cost.

More recently a new direction has been taken by WHO and other International Agencies since the International Conference on Primary Health Care in Alma Ata, USSR in 1978 (see also Chapter 1). The Alma Ata conference in 1978 introduced
the slogan aim of 'Health for all in the year 2000' (see Chapter 1) and outlined seven basic components of primary health care, including immunization, control of diarrhoeal and respiratory disease, maternal and child health with family planning, nutrition and potable water. Infectious viral disease plays a major and central role in this grand strategy and although immunization is highlighted as a major prophylactic approach nevertheless the use of antiviral drugs could, in the future, play a major role with certain viral diseases, particularly respiratory viruses. However, it is possible that a programme to eliminate a particular disease such as measles or
polio would not enjoy the international support required. Additionally, people in remote or poorly developed areas co-operated willingly in the smallpox programme but they may not be so enthusiastic about eliminating diseases such as polio or measles. It may well be the case that no other candidate viral disease for global eradication exists. We may have to be content with 'national' or 'area' eradication. Commenting on the 'Health for all by the year 2000', Dr. H. Mahler, Director General of WHO said "The present realities of the Third World are simply unacceptable. There is little joy in life nor any kind of justice for a child condemned to disease or early death because of the accident of birth in a developing country. Nor is there any rationale that can defend a system that continues to withhold the gift of health and care from 9/10ths of a nation's population. Smallpox eradication is a sign, a token of what can be achieved in breaking out of the cycle of ill health, disease and poverty. It comes as a glimpse into the future, an intimation of a viable new order of things, in which world health, meaning health for the world, will have central significance in an upward spiral of economic and social progress." (World Health, 1980).

15.5. Production of smallpox vaccine

Although smallpox has been eradicated from the world, batches of vaccinia vaccine (for prevention of smallpox) are still prepared and stored in some countries. Details of production, for example, are worth reiterating as an example of a highly successful virus vaccine, yet which, because of the relatively uncontrolled production methods and standardization would probably not be licensed today if proposed for a new vaccine. Currently used vaccine strains of vaccinia virus are neither cowpox nor mutants of variola virus, although they may be hybrids of these. The strains induce only mild dermal and systemic reactions as estimated by clinical observation in man. Jenner's original virus was maintained by arm to arm passage but this technique was discontinued after 1881, when large scale preparation of vaccine in calves was instituted. Up to the 1970s calves or sheep were used for vaccine production, the latter often preferred because of freedom from tuberculosis, small size, and docility (Turner, 1970). Under anaesthesia one flank is clipped and shaved and, after washing, lightly scarified with 8–10 ml of seed virus applied with a sterile scapula. Four days later the animals are exsanguinated, the vaccinated area is washed and dried with sterile towels. 50–100 g of pulp is removed by scraping with a large spoon and stored in liquid nitrogen. Each g of tissue contains up to $10^{18}$ virions and would thus represent approximately 2000 doses of vaccine. Treatment of the pulp with phenol at room temperature reduces bacterial counts without greatly diminishing virus titre. Virus may be easily extracted by fluorocarbon. Following examination for bacterial contamination and potency the material is used for glycerolated liquid vaccine (40% glycerol) and freeze dried. Virus is quantitated by titration on the
HOW MUCH DID IT COST to send a man to the Moon?
Between 1961, when President John Kennedy gave a directive to set a man on the Moon and bring him back "before this decade is over", and the successful landing in August 1969 of two men in the Sea of Tranquility and their safe return to Earth, the US space agency NASA is estimated to have spent
US $24,000 million
to wipe out smallpox from the Earth?
Between 1967, when WHO ordered its intensified Smallpox Eradication Programme into action, and 1980, when the Thirty-third World Health Assembly endorsed the final disappearance of this disease from the Earth, the total cost of eradication was
US $300 million
HOW MUCH WILL IT SAVE?
The estimated saving every year to all countries when smallpox vaccination is abolished worldwide is
US $1,000 million
HOW MANY VICTIMS WERE THERE?
In the one year 1967, official health statistic returns showed there were 131,697 cases of smallpox. But the figures showed only a tiny fraction of the real suffering. It is estimated that in that year there were
over 10 million cases
of smallpox in the world
HOW MANY PEOPLE DIED?
It is estimated that, in 1967, the death toll was
about two million people
HOW MANY PEOPLE WORKED TO SAVE THE WORLD FROM SMALLPOX?
The total number of national staff, in over 40 countries, who worked in the Smallpox Eradication Programme was
200,000 men and women
The total number of international staff, from more than 70 countries, was
about 700 men and women
HOW MANY SHOTS OF VACCINE?
Estimated total number of doses of smallpox vaccine used in the global programme:
Total produced by endemic countries: 2,000 million
Total distributed by WHO: 400 million
HOW MANY BIFURCATED NEEDLES?
Between 1967 and 1976 WHO supplied over 40 million needles to the programme. The needle was inspired by the basic sewing machine needle, the loop being ground down to produce the pronged fork. The advent of the bifurcated needle brought major savings in the quantity of vaccine required.

Fig. 15.5. A summary of financial and practical aspects of the smallpox eradication campaign. (from World Health, 1980.)
chick chorio allantoic membrane and 1 ml of vaccine should contain more than $10^8$ ID$_{50}$ of virus and less than $10^3$ microbial contaminants (none of them pathogens). It is unlikely, therefore, that this traditional smallpox vaccine would pass licensing requirements which could be required today! A new interesting proposal for the use of vaccinia as a vector for other virus antigens such as hepatitis B, polio or influenza is discussed in Chapter 2.

15.6. Chemotherapy

The need for chemotherapy against poxvirus infections in man has almost disappeared since the eradication of smallpox and the decreased use of vaccinia virus for vaccination. The rare orf and milkers nodes infections are not primary targets for antiviral chemotherapy. However, molluscum contagiosum is frequent enough to call for therapy but since it cannot be grown in cell culture or in animals the possibilities of developing drugs against this disease are very distant, and no work has been reported in this direction. Poxviruses induce a large number of enzymes (Table 15.2) including DNA polymerase and thymidine kinase of potential interest as targets for antiviral drugs. These enzymes have not been used in any published systematic search for inhibitors.

Possibly the first antiviral compound described in the literature was p-amino-benzaldehyde thiosemicarbazone which Brownlee and Hamre (1951) found to inhibit the multiplication of vaccinia virus. Among similar structures investigated, Bauer and Sadler (1960) found 1-methyl-1H-indole-2,3-dione-3-thiosemicarbazone (methisazone, Marboran®, Fig. 15.6) which is active against several different viruses in cell culture (Bauer et al., 1970). The mechanism of action of methisazone against poxvirus is not known in detail. It is not virucidal and does not affect virus adsorption. It is possible that the metal chelating properties of methisazone are of importance. The structure-activity relations for this type of compound are illustrated in Table 15.5 where the N-substituents are varied.

**Vaccinia infections**

The complications resulting from vaccination against smallpox in persons with eczema or immunological deficiencies have been treated with methisazone and gammaglobulin. Both these modalities seem to have therapeutic effects (see Bauer,

Fig. 15.6. Structural formula of methisazone.
TABLE 15.5.
Structure-activity relations for the anti-vaccinia activity of N-substituted isatin β-semithiocarbazones in cell culture (after Bauer and Sadler, 1960)

| N-substituent          | Relative antiviral activity |
|------------------------|----------------------------|
| None                   | 100                        |
| Methyl                 | 202                        |
| Ethyl                  | 286                        |
| Isopropyl              | 44                         |
| Propyl                 | 28.5                       |
| Pentyl                 | 3.4                        |
| Hydroxymethyl          | 42                         |
| 1-Methyl-4-trifluoromethyl | 48.4                   |
| 2-Hydroxyethyl         | 204                        |
| Acetyl                 | 87                         |
| Ethoxycarbonylmethyl   | 0                          |

1977). The availability of vaccinia immune globulin (VIG), prepared from revaccinated military personnel, will decrease as vaccination decreases. No controlled study on the efficacy of methisazone on vaccinia infections has been reported.

Smallpox
Methisazone has been used as a prophylactic agent in contacts exposed to patients suffering from smallpox. Bauer et al. (1969) conducted a prophylactic trial in Madras where contacts of variola major cases were given methisazone according to three different schedules. The results from this trial are summarized in Table 15.6 and clearly show that methisazone gave a significant ($P<0.001$) protection. However, in prophylactic trials carried out subsequently by Heiner et al. (1971) no significant effects were observed although there was a trend in favour of methisazone (Table 15.7). The difference in outcome could possibly be explained by different dosing of the drug. The last study was carried out using $2 \times 3$ mg methisazone with a short interval which might have induced vomiting and concomitant loss of drug. Two

TABLE 15.6.
Effect of methisazone treatment on the incidence of contact cases of smallpox. Methisazone was given prophylactically as $2 \times 3$ g/day, $2 \times 1.5$ g/day or $3$ g/day for 4 days (placebo was not generally given) (after Bauer et al., 1969)

| Group | Treatment                  | Contacts | Cases | Deaths | Case incidence (%) |
|-------|----------------------------|----------|-------|--------|-------------------|
| 1     | Treated, all dose levels   | 2292     | 6     | 2      | 0.26              |
| 2     | Not completed              | 318      | 12    | 2      | 3.77              |
| 1+2   | Total treated              | 2610     | 18    | 4      | 0.69              |
| 3     | Not taken                  | 150      | 11    | 3      | 7.33              |
| 4     | Not offered                | 2560     | 105   | 18     | 3.99              |
| 3+4   | Total untreated            | 2710     | 116   | 21     | 4.17              |
TABLE 15.7.
Effect of methisazone on attack rates in contact cases of smallpox. Adults were given two daily prophylactic doses of 3 g at intervals of four to six hours (doses for children were reduced) (after Heiner et al., 1971)

| Treatment          | Contacts | Cases | Deaths | Attack rate (%) |
|--------------------|----------|-------|--------|-----------------|
| Methisazone        |          |       |        |                 |
| Full dose          | 229      | 6     | 1      | 2.6             |
| Incomplete dose    | 13       | 0     | 0      | 0.0             |
| Vomited            | 20       | 1     | 0      | 5.0             |
| Total methisazone  | 262      | 7     | 1      | 2.7             |
| Placebo            | 260      | 13    | 2      | 5.0             |
| Other untreated    |          |       |        |                 |
| Refused            | 26       | 1     | 0      | 3.8             |
| Absent             | 22       | 0     | 0      | 0.0             |
| Total untreated    | 308      | 14    | 2      | 4.5             |

daily, well separated, doses of 3 g methisazone for 4 days might be expected to be optimal.

No therapeutic effect of methisazone or any other compound against smallpox has been reported. A double-blind study by Rao et al. (1969) showed no therapeutic effect of methisazone. It is possible that treatment institution in many patients may have been too late to be expected to change the course of the infection.

15.7. Summary

The global eradication of smallpox by vaccination is a milestone in preventative medicine. The smallpox vaccine also protects against monkeypox. Passive immunization can prevent complications from vaccination against smallpox. The antiviral compound in methisazone has a prophylactic, but not therapeutic, effect against smallpox.

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