fluenza nor those who have a qualified, if not negative, reaction to it, are in a position at present to demand acceptance of their particular view. On the basis of the recorded experiences of 1918, the circumstantial evidence that the swine-influenza virus may be the agent that caused the pandemic, I have taken the stand that it is probably safest to carry out mass prophylaxis later this year, when enough vaccine has become available to immunize the bulk of the population. The suggestion that it might be well to wait until there is evidence of disease due to this virus in other parts of the world is open to serious question. In the first place, it may well be, as it was in 1918, that a new pandemic will start in the United States. Moreover, even if the disease first appears in other parts of the globe, there may not be sufficient time to prepare enough of the immunizing agent to protect a sufficiently large segment of our population. In addition, it must be emphasized that experiences with the epidemiology of influenza over many years, but especially during the second wave of infection in 1918, point out very clearly that the disease may appear in widely separated areas of the world almost, if not, simultaneously. So, as in the early part of the century, influenza may again become a problem in as far distant cities as Bombay and Boston on the same day.

Two other questions require consideration. Who should be immunized? Should swine-influenza virus vaccine be monovalent? Although it has been proposed that the entire population of the United States be immunized, there is adequate evidence that young children, with the possible exception of those under one year of age, do not require such protection. Experience in 1918 and in subsequent epidemics and pandemics has indicated that influenza is a mild disease in youngsters under the age of 13 and that, in many cases, the infection is clinically inapparent and detected only when serial studies of levels of specific antibody are carried out. The premise that only those who account for excess mortality rates during outbreaks of influenza — persons with chronic heart (especially mitral stenosis) and pulmonary disease, people over the age of 50 years and pregnant women — may not be tenable for disease due to the porcine virus. Not only such patients but also a very large number of young (20 to 30 years of age), otherwise healthy persons sickened and died in 1918. This fact suggests that the "mass" to be immunized should include all persons older than 12 years. The possibility that pregnancy will increase the risk of potentially serious reactions to swine-influenza virus vaccine cannot be denied. However, it must be weighed against the increased frequency of maternal and fetal death observed in 1918 as well as in epidemics of the disease that have occurred since then.

It is probably best to include the swine-influenza virus in a vaccine containing other Type A and B strains known to have recently been involved in outbreaks of the disease. This precaution is necessary for two reasons: the next epidemic may not be caused by the porcine virus; and it is possible, although not very likely, that more than one viral type will be involved, and that both swine and human agents will produce infection in a given area simultaneously.

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THOU SHALT BE VACCINATED

WHAT does J.Q. (for Queasy) Healthsumer do when the President, flanked by Albert Sabin, Jonas Salk, and a host of co-experts, proclaims, "Thou shalt be vaccinated against the flu"? J.Q.H.'s response is predictable: he joins the legion of vaccinees — i.e., if he can get the vaccine in time.

On March 25, 1976, when the newspapers announced this new "war" on a given disease, details of how the decision was made were meager, and some readers had strong misgivings. Were, in fact, the viral experts summoned to Washington and told to support what a public-relations wizard had dreamed up as an election-year gimmick? And had the scientists had any chance to discuss the host of problems that might make the "war" resemble our campaign in Cambodia? As recently as April 6 this year, the *New York Times* editorialized on the doubts that linger in the minds of many.[1]

In the preceding editorial, however, Dr. Louis Weinstein, a senior statesman in infectious disease and unencumbered by political pressure and presidential prestige, reassures us by supporting pan-vaccination — except for children and those sensitive to egg white. The management of pregnant women poses a tough choice: in them, a reaction to vaccination may have more serious consequences, but in them, as well, the disease itself may be more serious.

In addition, fears that the medical scientists merely served the President as window dressing appear unwarranted. Indeed, at an earlier meeting in January plans had been laid for the containment of any viral epidemics that might threaten. Contrary to the impressions given by the rather skimpy news accounts at the time of the March 25 announcement, the decision was neither a response to an ultimatum nor a pro forma affair. All the questions mentioned by Dr. Weinstein, and others as well, were apparently well debated and not swept under the rug for political reasons.

Two basic, essentially philosophic aspects of the decision to engage in preventive war against the swine-influenza virus warrant recognition. Firstly, whatever the competence and involvement of the scientists present when the decision to vaccinate for swine influenza was made, and whatever the prestige of the individuals or groups that have lined up behind the plan, decisions of this type unavoidably are made under circumstances in which the principles of Pascal's Wager[2] predominate over those of objective decision analysis. What scientist can assure the President that a viral flu epidemic will not rage in 1976-77, or which expert can suggest an alternative and reasonably effective prophylactic measure? Under such circumstances, only one decision is practically and emotionally possible. If the vaccine is given and nothing happens — or even if there are a number of flu cases — no one will be blamed, and the decision makers may well be praised. But if vaccination is not recommended and an epidemic ensues.... What can anyone — expert or non-expert, President or J.Q.H. — do but hedge?

Secondly, is not the entire performance somewhat ironic in the light of our well publicized dedication to the principle of informed consent? Any physician is now well indoctrinated that, if he is inclined to vaccinate a given patient on

his own initiative, he is morally if not legally obligated to provide that patient with an adequate explanation of the pros and cons of his action, and then to elicit so-called informed consent. Yet when government acts, the very government whose deeds and attitudes are promoting the principle of informed consent, what happens? With bland indifference to either information or consent, the recommendation is made, "Thou shalt be vaccinated."

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CORRESPONDENCE

Letters to the Editor are welcomed and will be published, if found suitable, as space permits. Like other material submitted for publication, they must be typewritten in double spacing (including references), submitted in duplicate, must not exceed 1½ pages in length and will be subject to editing and possible abridgment.

LIVER-CELL ADENOMAS AND ORAL CONTRACEPTIVES

To the Editor: Edmondson et al. (N Engl J Med 294:470-472, 1976) have quite rightly called attention to the liver-cell adenomas that seem to be associated with oral contraceptives. Their discussion of the pathology of the lesion is helpful, but when they attempt to pinpoint exactly which estrogen might be responsible for the lesion, they may well have fallen into a statistical trap.

Among the patients in whom liver tumors developed, 10 out of 34 had been on the medication for more than nine years. On the other hand, of the control patients, 15 out of the 34 had been on the medication for less than 12 months. It is entirely possible, in other words, that the frequency with which mestranol appears among the "cases" simply reflects the marketing tendency of a period 10 years ago. Although I have no access to marketing figures, my memory is that 10 years ago, approximately 80 per cent of the oral contraceptives had mestranol whereas at present, the ratio between mestranol-bearing compounds and ethinyl estradiol compounds must be closer to 50-50. The frequency with which mestranol appears, in other words, may be simply a phenomenon of drug availability at the time when the patients (versus the controls) purchased their medication.

One would hope that the statistical basis for this observation could be re-examined with such a possibility in mind. Obviously, it would also be helpful if we knew how many of the control patients had clinical evidence of liver enlargement.

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To the Editor: The report by Baum and his colleagues[1] apparently initiated a series of publications on cases of liver-cell adenomas in women using oral contraceptives. Liver-cell adenomas are very rare tumors that had previously been found most frequently in women of the fertile age.[2,3] The evidence of an association between the widely used oral contraceptives and the occurrence of liver-cell adenomas obviously cannot rely on case reports. Using the technic of matched case-control pairs, Edmondson and his associates (N Engl J Med 294:470-472, 1976) made a very fine attempt to test the hypothesis derived from these cases. However, the valid conclusions achieved by this technic imply identical selection of cases and controls. I suggest that in the study by Edmondson et al., a selection bias may have been introduced because of the inclusion of cases received for pathological consultation from other institutions after 1973, the year of the report by Baum and his co-workers. After 1973 the probability that specimens of liver-cell adenomas were referred to Edmondson may have been selectively increased for the tumors found in women presenting long-term use of oral contraceptives.

The interpretation of the association, if true, should not be restricted to the possibility that the drug produces the tumor. In preexisting tumors the drug may increase the growth, friability or vascularity, thereby making the tumor more likely to be clinically manifest.

The incidence of liver-cell adenomas in women using oral contraceptives seems to be so low[4-6] that the possible association presumably should be of minor consideration in the general choice of oral contraceptive. It also seems an exaggerated precaution to examine and inform all women taking oral contraceptives about liver-cell adenomas. However, it may be prudent to discourage the use of oral contraceptives in women who have had or have a liver-cell adenoma.

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To the Editor: Reports in the lay press regarding the conclusions of the paper by Edmondson and his colleagues have been widely read and discussed. Although the conclusions reached in the article may be correct, the data presented omit critical factors that are necessary to substantiate those conclusions.

In a retrospective study one of the most critical factors in study design is the selection of the controls. The method of selection of controls in this paper is most unusual — that is, permitting the patient to select her own control. Although the patients appear to match well in age, age at menarche, number of pregnancies, etc., the critical match was neglected. The most critical factor would be a match of the year in which the patient and her control were taking the oral contraceptive. The manuscript does not make it clear precisely what span of time the study includes, but the year 1955 is mentioned as a possible beginning of the study and "the late 1960's" as a possible end point. If such a time span obtained, it is quite possible that the adenoma group took the oral contraceptives at an earlier year than the controls, and the great preponderance of mestranol use in the adenoma group and the ethinyl estradiol use in the control group could easily be explained by chance.

The oral contraceptives before 1964 all contained mestranol, and ethinyl estradiol was first introduced as an oral contraceptive in 1964. Marketing figures for oral contraceptive prescriptions show that until 1970, mestranol was used more frequently than ethinyl estradiol.

The paper certainly does reinforce existing data suggesting the relation of oral contraceptives and adenoma of the liver. However, on the evidence presented the implication that mestranol is more dangerous than ethinyl estradiol is, to say the least, tenuous.

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